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Identification of ten variants associated with risk of estrogen receptor negative breast cancer

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Most common breast cancer susceptibility variants have been identified through genome-wide association studies (GWASs) of predominantly estrogen receptor (ER)-positive disease¹. We conducted a GWAS using 21,468 ER-negative cases and 100,594 controls combined with 18,908 *BRCA1* mutation carriers (9,414 with breast cancer), all of European origin. We identified independent associations at $P < 5 \times 10^{-8}$ with 10 variants at nine novel loci. At $P < 0.05$, we replicated associations with 10 of 11 variants previously reported in ER-negative or *BRCA1* mutation carrier GWASs, and observed consistent associations with ER-negative disease for 105 susceptibility variants identified by other breast cancer GWASs. These 125 variants explain approximately 16% of the familial risk of this breast cancer subtype. There was high genetic correlation (0.72) between risk of ER-negative breast cancer and breast cancer risk for *BRCA1* carriers. These findings will likely lead to improved risk prediction and inform further fine-mapping and functional work to better understand the biological basis of ER-negative breast cancer.

GWASs have identified 107 single nucleotide polymorphisms (SNPs) that are independently associated with breast cancer risk²⁻³². Association studies focused on ER-negative disease, or *BRCA1* mutation carriers, who are more likely to develop ER-negative disease (70-80% of cases)³³, have identified 11 of these SNPs^{3,9,12,19,29,30}. We aimed to discover additional ER-negative breast cancer susceptibility variants by performing a GWAS in women of European origin.

New genotyping data were generated for 9,655 ER-negative cases and 45,494 controls from 68 Breast Cancer Association Consortium (BCAC) studies and 15,566 *BRCA1* mutation carriers (7,784 with breast cancer) from 58 Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) studies (Supplementary Tables 1 and 2) using the Illumina OncoArray beadchip, a 570K SNP custom array with genome-wide coverage³⁴. Imputation was used to derive estimated genotypes for ~21M SNPs, using the 1000 Genomes Project (Phase 3) as reference; ~11.5M of those with imputation $r^2 > 0.3$ and minor allele frequency (MAF) > 0.005 were included in further analyses. For BCAC data, we estimated per-allele odds ratios (ORs) using logistic regression, adjusting for country and principal components. For CIMBA data, we estimated per-allele hazard ratios (HR) using a retrospective cohort analysis framework, modelling time to breast cancer and stratifying on country, Ashkenazi Jewish origin and birth cohort^{35,36} (see Online Methods). These analyses were also applied to an independent set of previously generated data from other genome-wide genotyping of additional European participants in 44 BCAC studies (11,813 ER-negative cases and 55,100 controls)^{9,12,16,20,37,38} and 54 CIMBA studies (3,342 *BRCA1* mutation carriers, 1,630 with breast cancer) (Supplementary Tables 1 and 2). Fixed-effects meta-analysis was used to combine results across genotyping initiatives within consortia and, assuming that the OR and HR estimates approximate the same underlying relative risk, across consortia³⁹.

Results from the combined meta-analysis are summarised in Supplementary Figures 1 and 2. There was minimal inflation of test statistics ($\lambda_{1000} = 1.004$;

Supplementary Figure 3). We identified 10 variants at nine novel loci that were independently associated with risk of ER-negative breast cancer at $P < 5 \times 10^{-8}$ (Table 1; Supplementary Table 3; Supplementary Figures 4-11). Two independent signals were observed within 12kb at 11q22.3, for rs74911261 (MAF=0.02) and rs11374964 (MAF=0.42); OR estimates and statistical significance were largely unchanged when each variant was adjusted for the other (Supplementary Table 4). The association with 8p23.3-rs66823261 was not observed for *BRCA1* mutation carriers ($P=0.32$, P -heterogeneity=0.030).

For each of these 10 novel signals, we identified candidate causal SNPs analytically^{40,41} (see Online Methods) and combined multiple sources of *in silico* functional annotation from public databases⁴²⁻⁵² to identify likely functional variants and target genes. Results are summarised in Supplementary Table 5 (including UCSC Genome Browser links; see also Supplementary Note), Figure 1 and Supplementary Figures 4-11 (data sources in Supplementary Table 6). Many candidate causal SNPs lie in predicted regulatory regions and are associated with expression of nearby genes in blood or other tissues. At 2p23, the predicted target genes include *ADCY3* and *NCOA1* (Supplementary Figure 4). At 6q23.1 (Supplementary Figure 5), the most plausible target gene is *L3MBTL3*⁵³. A predicted target at 8q24.13 is *FBXO32*, which is expressed in ER-negative HMECs but not ER-positive MCF7 breast cancer cells (Supplementary Figure 7) and has a known role in cancer cachexia⁵⁴. At 11q22.3 (Figure 1), a predicted target gene of common risk-associated variants is *NPAT*⁵⁵. The rarer SNPs underlying the other 11q22.3 signal are predicted to target *ATM*, a known breast cancer susceptibility gene⁵⁶. Three rare coding variants (MAF \leq 0.03) in *ATM*, *NPAT* and *KDELC2*, are also among the candidate causal SNPs at this locus. At 16p13, predicted target genes include *ADCY9* and *CREBBP* (Supplementary Figure 8). At 19q12 (Supplementary Figure 11), a potential target gene encodes cyclin E1 which is involved in cell cycle control and phosphorylation of NPAT⁵⁷.

Expression QTL associations were assessed between each candidate causal variant and genes within 1Mb using 79 ER-negative breast tumours from TCGA and 135 normal breast tissue samples from METABRIC⁵⁸⁻⁶⁰. The strongest associations identified were 6q23.1-rs6569648-*L3MBTL3* ($P=4.3 \times 10^{-6}$) and 18q12.1-rs12965632-*CDH2* ($P=1.0 \times 10^{-4}$), both in METABRIC (Supplementary Table 5). SNP rs6569648 was the top *cis*-eQTL (of all imputed variants within 1 Mb) for *L3MBTL3* while the *p*-value for the rs12965632-*CDH2* eQTL was within two orders of magnitude of the top *cis*-eQTLs for this gene (Supplementary Figures 12-13).

For 10 of the 11 variants previously identified through GWASs of ER-negative disease or overall disease in *BRCA1* mutation carriers^{3,9,12,18,19,30,31}, or reported as more strongly associated with ER-negative breast cancer²⁹, associations with ER-negative disease were replicated ($P < 0.05$) using OncoArray data from BCAC, which does not overlap with any of the discovery studies (Table 2). Effect sizes were generally similar to those originally reported. Using all available CIMBA data, six of these 11 variants were associated with breast cancer risk ($P < 0.05$) for *BRCA1* mutation carriers (Table 2). No evidence of association was observed for 20q11-rs2284378¹² in either BCAC or CIMBA ($P \geq 0.46$).

Based on estimated ORs using BCAC data for all cases with known ER status (16,988 ER-negative; 65,275 ER-positive), all 10 new and 10 previously reported

and replicated ER-negative disease susceptibility SNPs were more strongly associated with risk of ER-negative than ER-positive subtype (P -heterogeneity <0.05 , except for novel hit 19p13.2-rs322144; Supplementary Table 7). Two variants (1q32.1-rs4245739 and 19p13.11-rs67397200) were not associated with ER-positive disease. For four variants (11q22.3-rs11374964, 11q22.3-rs74911261, 1q32.1-rs6678914 and 2p23.2-rs4577244), the risk-associated allele for ER-negative disease was associated with reduced risk of ER-positive disease ($P<0.05$).

For these 20 ER-negative breast cancer susceptibility SNPs, we also assessed associations by triple-negative (TN) status (negative for ER, progesterone receptor and HER2; Table 3), tumour grade (Table 4) and age at diagnosis (Supplementary Table 8) using BCAC data only. Five, including the novel susceptibility variants 11q22.3-rs11374964 and 11q22.3-rs74911261, were more strongly associated with risk of both TN and higher-grade disease ($P<0.05$), although after adjustment for TN status, heterogeneity by grade was observed only for 11q22.3-rs74911261 and 1q32.1-rs4245739 ($P<0.05$). For 2p23.3-rs4577244, heterogeneity was observed for grade only, while 6q25.2-rs2747652 was more strongly associated with risk of other (non-TN) ER-negative breast cancer subtypes ($P<0.05$). At younger ages, associations appeared to be stronger for two variants (5p15.33-rs10069690 and 19p13.11-rs67397200), and weaker for one (6q25.2-rs2747652) ($P<0.05$).

Elsewhere we report 65 novel susceptibility loci for overall breast cancer¹. Three of these overlap within 500kb with the novel ER-negative disease-associated loci reported here (variants 2p23.3-rs200648189, 6q23.1-rs6569648 and 8q24.13-rs17350191). We assessed associations with risk of ER-negative disease, and with risk of overall breast cancer for *BRCA1* mutation carriers, for SNPs at the remaining 62 loci, as well as for the 96 previously reported breast cancer susceptibility variants that were not ER-negative specific. Of these 158 SNPs, 105 were associated ($P<0.05$) with risk of ER-negative breast cancer, and 24 with risk for *BRCA1* mutation carriers (Supplementary Tables 9-10). Results for *BRCA2* mutation carriers are presented in Supplementary Table 11.

Pathway analysis based on mapping each SNP to the nearest gene was performed using summary association statistics from the meta-analysis of BCAC and CIMBA data combined⁶¹⁻⁶⁴ (see Online Methods). This identified several pathways implicated in ER-negative disease (enrichment score [ES] ≥ 0.41 ; Supplementary Figure 14; Supplementary Tables 12-13), including a subset that was not enriched in susceptibility to ER-positive disease ($ES<0$; Supplementary Table 14). One of the latter subsets was the adenylate cyclase (AC) activating pathway ($ES=0.62$; Supplementary Figure 15). Two of the predicted target genes for the 10 novel ER-negative breast cancer susceptibility variants, based on the eQTL analysis (Supplementary Table 5), *ADCY3* ($P[TCGA]=6.7\times 10^{-3}$) and *ADCY9* ($P[METABRIC]=1.3\times 10^{-4}$), are part of this pathway, and their association signals were critical to the elevated ES observed (Supplementary Figure 14). *ADCY9* is stimulated by $\beta 2$ adrenergic receptor ($\beta 2AR$) signalling⁶⁵ in ER-negative breast cancer⁶⁶, which in turn drives AC-cAMP signalling, including for example mitogenic signalling through β -arrestin-Src-ERK⁶⁷.

To further explore the functional properties of the genome that contribute to ER-negative breast cancer heritability, we conducted a partitioned heritability analysis using linkage disequilibrium (LD) score regression⁶⁸. Considering 52 “baseline”

genomic features, we observed the greatest enrichment for super-enhancers (2.5-fold, $p=2 \times 10^{-7}$) and the H3K4me3 histone mark (2.4-fold, $p=0.0005$), with 33% depletion ($p=0.0002$) observed for repressed regions (Supplementary Table 15). No differences in enrichment for these features were observed between susceptibility to ER-negative and ER-positive breast cancer, but baseline genomic features are not specific to cell type⁶⁸. The estimated correlation between ER-negative and ER-positive breast cancer based on ~1M common genetic variants^{69,70} was 0.60 (standard error [SE], 0.03) indicating that, although these two breast cancer subtypes have a shared genetic component, a substantial proportion is distinct. The estimated correlation between ER-negative disease in the general population and overall breast cancer for *BRCA1* mutation carriers was 0.72 (SE, 0.11).

In summary, in this study of women of European origin, we have identified 10 novel susceptibility variants for ER-negative breast cancer and replicated associations with ER-negative disease for 10 SNPs identified by previous GWASs. Most of these were not associated, or more weakly associated, with ER-positive disease, consistent with the findings from pathway and partitioned heritability analyses showing that ER-negative breast cancer has a partly distinct genetic aetiology. We also observed consistent associations with ER-negative disease for a further 105 overall breast cancer susceptibility SNPs. Together, these 125 variants explain ~14% of an assumed 2-fold increased risk of developing ER-negative disease for the first degree female relatives of women affected with this subtype (the newly identified SNPs explain ~1.5%); Supplementary Table 16) and ~40% of the estimated familial risk that is attributable to all variants imputable from the Oncoarray (see Online Methods). We have also identified nine novel breast cancer susceptibility variants for *BRCA1* mutation carriers and confirmed associations for a further 30 previously reported SNPs; these 39 variants explain ~8% of the variance in polygenic risk for carriers of these mutations (Supplementary Table 17). However, the lower number of *BRCA1* risk-associated variants may merely be a consequence of the smaller sample size, since the genetic correlation with ER-negative breast cancer is high. These findings will likely inform improved risk prediction, both for the general population and for *BRCA1* mutation carriers^{30,71,72}. Further investigation is required for other populations of non-European origin. Fine-mapping and functional studies should lead to a better understanding of the biological basis of ER-negative breast cancer, and perhaps inform the design of more effective preventive interventions, early detection and treatments for this disease.

Data availability

A subset of the data that support the findings of this study is publically available via dbGaP (see URLs section; accession number phs001265.v1.p1). The complete dataset will not be made publically available due to restraints imposed by the ethics committees of individual studies; requests for data can be made to the corresponding author or the Data Access Coordination Committees (DACCs) of BCAC (see URLs section) and CIMBA (see URLs section). BCAC DACC approval is required to access data from studies ABCFS, ABCS, ABCTB, BBCC, BBS, BCEES, BCFR-NY, BCFR-PA, BCFR-UT, BCINIS, BSUCH, CBCS, CECILE, CGPS, CTS, DIETCOMPLYF, ESTHER, GC-HBOC, GENICA, GEPARSIXTO, GESBC, HABCS, HCSC, HEBBS, HMBCS, HUBCS, KARBAC, KBCP, LMBC, MABCS,

MARIE, MBCSG, MCBSC, MISS, MMHS, MTLGEBSC, NC-BCFR, OFBCR, ORIGO, pKARMA, POSH, PREFACE, RBCS, SKKDKFZS, SUCCESSB, SUCCESSC, SZBCS, TNBCC, UCIBCS, UKBGS and UKOPS (see Supplementary Table 1). CIMBA DACC approval is required to access data from studies BCFR-ON, CONSTIT TEAM, DKFZ, EMBRACE, FPGMX, GC-HBOC, GEMO, G-FAST, HEBSC, HEBON, IHCC, INHERIT, IOVHBOCS, IPOBCS, MCGILL, MODSQUAD, NAROD, OCGN, OUH and UKGRFOCR (see Supplementary Table 2).

URLs

dbGaP: <https://www.ncbi.nlm.nih.gov/gap>
BCAC: <http://bcac.ccge.medschl.cam.ac.uk/>
CIMBA: <http://cimba.ccge.medschl.cam.ac.uk/>
PCcalc software: <http://ccge.medschl.cam.ac.uk/software/pccalc/>
SNPTEST: https://mathgen.stats.ox.ac.uk/genetics_software/snptest/snptest.html
GeneSets: <http://baderlab.org/GeneSets>
GenGen package: <http://gengen.openbioinformatics.org/en/latest/>

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Competing Financial Interests

The authors confirm that they have no competing financial interests

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Figure legends

Figure 1. Genomic region around independent ER negative risk associated variants, 11_108345515_G_A (rs11374964) and 11_108357137_G_A (rs74911261). One Mb region showing statistical significance of all genotyped and imputed SNPs and positions of candidate causal variants for two independent signals (shown below as red or blue ticks) in relation to RefSeq genes. Missense variants are labelled with asterisks. Breast cell enhancers overlapping candidate SNPs predicted to target nearby genes by IM-PET⁴⁶ are depicted as black bars. Chromatin interactions from ENCODE ChIA-PET in MCF7 cells overlapping candidate variants are shaded to reflect interaction confidence scores. Epigenomic features (derived from publicly available ChIP-seq and DNase-seq) that overlap candidate variants are shown as red or blue segments, depending on the intersected signal. Density tracks show the summed occurrence of ChIP-seq and DNase-seq peak signals at each position. Roadmap Epigenomics Project chromatin state models for HMEC and myoepithelial cells grouped into enhancer, promoter or transcribed annotations are shown as yellow, red or green segments, respectively. Transcript levels in MCF7 and HMEC cells are represented by histograms depicting mean normalised RNA-seq expression. All MCF7 ChIA-PET (ENCODE) and HMEC Hi-C⁴⁷ chromatin interactions are represented by black and blue arcs, respectively. NHGRI catalog GWAS SNPs are shown as green ticks. All Oncoarray SNPs (genotyped or imputed) are shown as black ticks and uninterrogated, common SNPs (dbSNP138, EUR MAF > 1%) as red ticks. Features may be examined in detail via exploration of a custom UCSC Genome Browser session accessible via hyperlinks within Supplementary Table 5.

Table 1: Ten novel loci associated with risk of estrogen receptor (ER)-negative breast cancer using meta-analysis of BCAC and CIMBA data

Location	SNP	Chr	Position	Nearest gene	Alleles [#]	BCAC ER-negative [†]			CIMBA <i>BRCA1</i> mutation carriers [‡]			Meta-analysis	Heterogeneity
						MAF	OR (95%CI)	P-value	MAF	HR (95%CI)	P-value	P-value	P-value [*]
2p23.3	rs200648189	2	24739694	<i>NCOA1</i>	CT/C	0.19	0.94 (0.91-0.97)	4.7x10 ⁻⁴	0.20	0.88 (0.84-0.92)	3.3x10 ⁻⁷	9.7x10 ⁻⁹	2.0x10 ⁻²
6q23.1	rs6569648	6	130349119	<i>L3MBTL3</i>	T/C	0.23	0.93 (0.90-0.95)	4.3x10 ⁻⁸	0.22	0.94 (0.90-0.98)	5.4x10 ⁻³	8.3x10 ⁻¹⁰	0.64
8p23.3	rs66823261	8	170692	<i>RPL23AP53</i>	T/C	0.23	1.09 (1.06-1.12)	5.6x10 ⁻⁹	0.22	1.02 (0.98-1.07)	0.32	3.3x10 ⁻⁸	3.0x10 ⁻²
8q24.13	rs17350191	8	124757661	<i>ANXA13</i>	C/T	0.34	1.07 (1.04-1.09)	2.0x10 ⁻⁸	0.34	1.08 (1.04-1.12)	1.9x10 ⁻⁴	1.7x10 ⁻¹¹	0.81
11q22.3	rs11374964	11	108345515	<i>KDELC2</i>	G/GA	0.42	0.94 (0.92-0.96)	3.6x10 ⁻⁸	0.43	0.91 (0.88-0.95)	1.3x10 ⁻⁶	4.1x10 ⁻¹³	0.26
11q22.3	rs74911261	11	108357137	<i>KDELC2</i>	G/A	0.02	0.82 (0.75-0.89)	2.3x10 ⁻⁶	0.02	0.74 (0.65-0.84)	2.0x10 ⁻⁶	5.4x10 ⁻¹¹	0.17
16p13.3	rs11076805	16	4106788	<i>ADCY9</i>	C/A	0.25	0.92 (0.90-0.95)	2.2x10 ⁻⁸	0.25	0.96 (0.92-1.00)	0.073	1.4x10 ⁻⁸	0.14
18q12.1	rs36194942	18	25401204	<i>CDH2</i>	A/AT	0.30	0.94 (0.91-0.96)	2.5x10 ⁻⁷	0.31	0.95 (0.91-0.99)	1.4x10 ⁻²	1.4x10 ⁻⁸	0.50
19p13.2	rs322144	19	11423703	<i>TSPAN16</i>	C/G	0.47	0.95 (0.93-0.97)	2.4x10 ⁻⁵	0.46	0.92 (0.89-0.96)	3.7x10 ⁻⁵	7.4x10 ⁻⁹	0.23
19q12	rs113701136	19	30277729	<i>CCNE1</i>	C/T	0.32	1.07 (1.04-1.09)	1.7x10 ⁻⁷	0.32	1.05 (1.01-1.09)	1.2x10 ⁻²	6.8x10 ⁻⁹	0.57

[#]More common allele listed first, minor allele second; [†]Combined data from 21,468 ER-negative cases and 100,594 controls of European ancestry from the Breast Cancer Association Consortium (BCAC); [‡]Combined data from 18,908 *BRCA1* mutation carriers from the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA), 9,414 of whom had developed breast cancer; ^{*}Test for heterogeneity in effect size for ER-negative disease and overall disease for *BRCA1* mutation carriers

Chr, chromosome; MAF, minor allele frequency; OR, odds ratio per copy of the minor allele; CI, confidence interval; HR, hazard ratio per copy of the minor allele

Table 2: Previously reported estrogen receptor (ER)-negative hits: replication using independent data from BCAC and combined results using all BCAC and CIMBA data

Location	SNP	Chr	Position	Ref	Nearest gene	Alleles [#]	INDEPENDENT REPLICATION			ALL AVAILABLE DATA COMBINED			
							BCAC ER-negative (OncoArray)*			BCAC ER-negative [†]		CIMBA <i>BRCA1</i> [‡]	
							MAF	OR (95%CI)	P-value	OR (95%CI)	P-value	HR (95%CI)	P-value
1q32.1	rs6678914	1	202187176	¹⁹	<i>LGR6</i>	G/A	0.41	0.94 (0.91-0.97)	1.1x10 ⁻⁴	0.92 (0.90-0.94)	2.6x10 ⁻¹²	0.98 (0.95-1.02)	0.31
1q32.1	rs4245739	1	204518842	¹⁹	<i>MDM4</i>	A/C	0.26	1.12 (1.09-1.17)	9.2x10 ⁻¹¹	1.14 (1.11-1.16)	3.1x10 ⁻²³	1.09 (1.04-1.13)	7.3x10 ⁻⁵
2p24.1	rs12710696	2	19320803	¹⁹	<i>MIR4757</i>	C/T	0.37	1.04 (1.00-1.07)	2.5x10 ⁻²	1.06 (1.04-1.09)	6.5x10 ⁻⁸	1.01 (0.98-1.05)	0.49
2p23.2	rs4577244 [‡]	2	29120733	³⁰	<i>WDR43</i>	C/T	0.34	0.93 (0.89-0.96)	9.6x10 ⁻⁵	0.92 (0.90-0.95)	1.5x10 ⁻⁹	0.92 (0.88-0.96)	1.3x10 ⁻⁴
5p15.33	rs10069690	5	1279790	^{9,18}	<i>TERT</i>	C/T	0.26	1.19 (1.14-1.23)	3.8x10 ⁻²¹	1.18 (1.15-1.21)	1.5x10 ⁻³⁵	1.18 (1.14-1.23)	3.7x10 ⁻¹⁶
6q25.1	rs3757322 [‡]	6	151942194	²⁹	<i>ESR1</i>	T/G	0.32	1.14 (1.10-1.18)	5.5x10 ⁻¹⁴	1.15 (1.12-1.18)	2.8x10 ⁻³¹	1.14 (1.10-1.19)	2.9x10 ⁻¹²
6q25.2	rs2747652 [‡]	6	152437016	²⁹	<i>ESR1</i>	C/T	0.48	0.92 (0.89-0.95)	1.1x10 ⁻⁷	0.91 (0.89-0.93)	1.9x10 ⁻¹⁸	1.00 (0.97-1.04)	0.96
13q22.1	rs6562760 [‡]	13	73957681	³⁰	<i>KLF5</i>	G/A	0.24	0.92 (0.88-0.95)	5.0x10 ⁻⁶	0.92 (0.90-0.95)	8.7x10 ⁻¹⁰	0.89 (0.86-0.93)	3.5x10 ⁻⁷
16q12.2	rs11075995	16	53855291	¹⁹	<i>FTO</i>	T/A	0.30	1.07 (1.03-1.11)	3.3x10 ⁻⁴	1.09 (1.06-1.12)	1.0x10 ⁻¹⁰	1.01 (0.97-1.06)	0.49
19p13.11	rs67397200	19	17401404	^{3,31}	<i>ANKLE1</i>	C/G	0.32	1.17 (1.13-1.21)	7.0x10 ⁻²⁰	1.17 (1.14-1.19)	2.7x10 ⁻³⁷	1.18 (1.14-1.23)	2.7x10 ⁻¹⁷
20q11.21	rs2284378	20	32588095	¹²	<i>RALY</i>	C/T	0.32	0.99 (0.95-1.02)	0.46	1.03 (1.01-1.06)	1.7x10 ⁻²	1.00 (0.97-1.04)	0.81

[#]More common allele listed first, minor allele second; ^{*}Includes Breast Cancer Association Consortium (BCAC) OncoArray data from 9,655 ER-negative cases and 45,494 controls cases and controls not included in previously published studies; [†]Combined data from 21,468 ER-negative cases and 100,594 controls of European ancestry from BCAC, which includes overlapping samples with previous publications for all SNPs; [‡]Combined data from 18,908 *BRCA1* mutation carriers from the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA), 9,414 of whom had developed breast cancer - includes overlapping samples with previous publications for SNPs rs4577244, rs3757322, rs2747652 and rs6562760

Chr, chromosome; Ref, publication(s) in reference list in which the association was identified; MAF, minor allele frequency; OR, odds ratio per copy of the minor allele; CI, confidence interval; HR, hazard ratio per copy of the minor allele

Table 3: Associations for 10 novel and 10 previously reported (and replicated) ER-negative breast cancer susceptibility loci, by triple-negative status (BCAC data only: ER-negative cases*, all controls))

Location	SNP	Triple-negative		Other ER-negative		Heterogeneity
		OR (95%CI)	P-value	OR (95%CI)	P-value	P-value*
Loci identified by the present study						
2p23.3	rs200648189	0.95 (0.90-1.00)	4.8x10 ⁻²	0.96 (0.91-1.03)	0.24	0.36
6q23.1	rs6569648	0.93 (0.89-0.97)	1.4x10 ⁻³	0.93 (0.88-0.98)	5.6x10 ⁻³	0.91
8p23.3	rs66823261	1.11 (1.05-1.16)	3.3x10 ⁻⁵	1.12 (1.07-1.19)	2.4x10 ⁻⁵	0.91
8q24.13	rs17350191	1.07 (1.03-1.11)	7.9x10 ⁻⁴	1.07 (1.02-1.12)	4.0x10 ⁻³	0.67
11q22.3	rs11374964	0.88 (0.85-0.91)	1.9x10 ⁻¹¹	0.99 (0.95-1.04)	0.75	1.5x10 ⁻⁵
11q22.3	rs74911261	0.76 (0.66-0.87)	1.1x10 ⁻⁴	0.98 (0.84-1.13)	0.76	3.0x10 ⁻²
16p13.3	rs11076805	0.91 (0.87-0.96)	1.5x10 ⁻⁴	0.95 (0.90-1.00)	4.5x10 ⁻²	0.20
18q12.1	rs36194942	0.93 (0.89-0.96)	2.4x10 ⁻⁴	0.92 (0.88-0.97)	9.9x10 ⁻⁴	0.94
19p13.2	rs322144	0.94 (0.91-0.98)	5.9x10 ⁻³	0.94 (0.90-0.98)	9.7x10 ⁻³	0.68
19q12	rs113701136	1.10 (1.06-1.15)	9.1x10 ⁻⁷	1.07 (1.02-1.12)	4.4x10 ⁻³	0.12
Previously reported loci (associations replicated by the present study)						
1q32.1	rs6678914	0.94 (0.91-0.98)	2.1x10 ⁻³	0.91 (0.87-0.95)	2.0x10 ⁻⁵	0.45
1q32.1	rs4245739	1.18 (1.13-1.23)	4.3x10 ⁻¹⁵	1.04 (1.00-1.10)	7.5x10 ⁻²	6.5x10 ⁻⁴
2p24.1	rs12710696	1.07 (1.03-1.11)	1.1x10 ⁻³	1.04 (1.00-1.09)	6.1x10 ⁻²	0.52
2p23.2	rs4577244	0.90 (0.86-0.94)	5.3x10 ⁻⁶	0.94 (0.89-0.99)	1.9x10 ⁻²	0.15
5p15.33	rs10069690	1.28 (1.23-1.33)	2.4x10 ⁻³³	1.07 (1.02-1.12)	5.4x10 ⁻³	5.6x10 ⁻⁸
6q25.1	rs3757322	1.15(1.10-1.19)	4.3x10 ⁻¹²	1.14(1.10-1.20)	4.8x10 ⁻⁹	0.35
6q25.2	rs2747652	0.93(0.89-0.96)	5.7x10 ⁻⁵	0.87(0.83-0.91)	2.9x10 ⁻¹⁰	9.6x10 ⁻³
13q22.1	rs6562760	0.94 (0.90-0.98)	2.8x10 ⁻³	0.92 (0.87-0.96)	8.8x10 ⁻⁴	0.46
16q12.2	rs11075995	1.06 (1.02-1.11)	6.5x10 ⁻³	1.08 (1.03-1.13)	3.1x10 ⁻³	0.81
19p13.11	rs67397200	1.27 (1.22-1.32)	2.0x10 ⁻³²	1.05 (1.01-1.10)	2.7x10 ⁻²	4.7x10 ⁻¹⁰

*Combined Breast Cancer Association Consortium (BCAC) data from 6,877 triple-negative and 4,467 other ER-negative cases and 83,700 controls; *ER-negative case-only analysis, by triple-negative status; OR, odds ratio per copy of the minor allele; CI, confidence interval

Table 4: Associations for 10 novel and 10 previously reported (and replicated) ER-negative breast cancer susceptibility loci, by grade (BCAC data only: ER-negative cases*, all controls)

Location	SNP	Grade 1		Grade 2		Grade 3		Heterogeneity
		OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value	P-value*
Loci identified by the present study								
2p23.3	rs200648189	1.11 (0.92-1.33)	0.28	0.95 (0.88-1.03)	0.23	0.96 (0.91-1.00)	6.8x10 ⁻²	0.70
6q23.1	rs6569648	0.93 (0.79-1.09)	0.37	0.93 (0.87-0.99)	1.6x10 ⁻²	0.94 (0.91-0.98)	3.8x10 ⁻³	0.34
8p23.3	rs66823261	1.13 (0.96-1.34)	0.14	1.12 (1.04-1.19)	1.2x10 ⁻³	1.10 (1.05-1.15)	1.3x10 ⁻⁵	0.11
8q24.13	rs17350191	1.16 (1.01-1.34)	3.0x10 ⁻²	1.05 (0.99-1.11)	0.10	1.09 (1.05-1.12)	4.1x10 ⁻⁶	0.94
11q22.3	rs11374964	0.91 (0.79-1.04)	0.16	0.99 (0.94-1.05)	0.85	0.93 (0.90-0.96)	1.3x10 ⁻⁵	3.0x10 ⁻²
11q22.3	rs74911261	1.22 (0.81-1.84)	0.35	0.89 (0.73-1.07)	0.21	0.74 (0.65-0.85)	7.4x10 ⁻⁶	6.7x10 ⁻⁴
16p13.3	rs11076805	0.90 (0.76-1.06)	0.21	0.93 (0.87-0.99)	3.2x10 ⁻²	0.92 (0.88-0.95)	4.5x10 ⁻⁵	0.71
18q12.1	rs36194942	0.97 (0.84-1.13)	0.73	0.93 (0.88-0.99)	2.2x10 ⁻²	0.96 (0.92-0.99)	2.3x10 ⁻²	0.98
19p13.2	rs322144	0.94 (0.81-1.08)	0.38	0.95 (0.90-1.01)	0.11	0.96 (0.93-1.00)	6.4x10 ⁻²	0.48
19q12	rs113701136	1.02 (0.89-1.18)	0.77	1.06 (1.01-1.13)	3.0x10 ⁻²	1.10 (1.06-1.14)	2.5x10 ⁻⁷	0.12
Previously reported loci (associations replicated by the present study)								
1q32.1	rs6678914	0.95 (0.83-1.09)	0.46	0.90 (0.85-0.95)	9.3x10 ⁻⁵	0.92 (0.89-0.95)	1.2x10 ⁻⁶	0.75
1q32.1	rs4245739	1.02 (0.88-1.19)	0.75	1.05 (0.99-1.12)	8.7x10 ⁻²	1.18 (1.14-1.22)	2.5x10 ⁻¹⁸	4.3x10 ⁻⁵
2p24.1	rs12710696	1.08 (0.94-1.23)	0.28	1.10 (1.04-1.16)	9.6x10 ⁻⁴	1.04 (1.01-1.08)	1.6x10 ⁻²	0.28
2p23.2	rs4577244	1.02 (0.88-1.20)	0.77	0.95 (0.89-1.01)	9.4x10 ⁻²	0.90 (0.86-0.93)	1.2x10 ⁻⁷	4.0x10 ⁻²
5p15.33	rs10069690	0.96 (0.83-1.12)	0.64	1.07 (1.01-1.14)	2.2x10 ⁻²	1.21 (1.17-1.26)	1.5x10 ⁻²⁴	7.3x10 ⁻⁴
6q25.1	rs3757322	1.16 (1.01-1.34)	0.04	1.13 (1.07-1.20)	7.5x10 ⁻⁶	1.18 (1.14-1.22)	4.5x10 ⁻²⁰	0.16
6q25.2	rs2747652	0.86 (0.75-0.98)	0.02	0.92 (0.87-0.97)	1.9x10 ⁻³	0.90 (0.87-0.93)	1.6x10 ⁻⁹	0.61
13q22.1	rs6562760	0.98 (0.84-1.15)	0.82	0.92 (0.87-0.98)	1.4x10 ⁻²	0.91 (0.88-0.95)	1.2x10 ⁻⁵	0.52
16q12.2	rs11075995	1.16 (1.00-1.35)	4.7x10 ⁻²	1.09 (1.02-1.15)	7.5x10 ⁻³	1.08 (1.04-1.13)	5.2x10 ⁻²⁸	0.42
19p13.11	rs67397200	1.01 (0.87-1.16)	0.91	1.08 (1.02-1.14)	9.8x10 ⁻³	1.22 (1.18-1.26)	5.3x10 ⁻³⁷	1.3x10 ⁻³

*Combined Breast Cancer Association Consortium (BCAC) data from 492 grade 1, 3,243 grade 2 and 8,568 grade 3 cases and 82,347 controls; * ER-negative case-only analysis of BCAC data, by grade (trend test, 1df); OR, odds ratio per copy of the minor allele; CI, confidence interval

Online Methods

Study subjects

Supplementary Table 1 summarises the studies from the Breast Cancer Association Consortium (BCAC) that contributed data. The majority were case-control studies. Sixty-eight BCAC studies participated in the ER-negative breast cancer component of the OncoArray, contributing 9,655 cases and 45,494 controls. All studies provided core data on disease status and age at diagnosis/observation, and the majority provided information on clinico-pathological and lifestyle factors, which have been curated and incorporated into the BCAC database (version 6). Estrogen receptor status for most (~70%) cases was obtained from clinical records. After removal of overlapping participants, genotype data were also available from eight GWASs^{9,12,16,37,38} (4,480 ER-negative cases and 12,632 controls) and 40 studies previously genotyped using the Illumina iCOGS custom array²⁰ (7,333 ER-negative cases and 42,468 controls).

A total of 21,468 ER-negative cases were included in the combined analyses. Of those 5,793 had tumours that were also negative for progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) and were defined as triple-negative (TN). PR and HER2 status was also obtained predominantly from clinical records. A further 4,217 were positive for PR or HER and were considered non-TN. The remainder had unknown PR or HER status. All participating studies were approved by their appropriate ethics review boards and all subjects provided informed consent.

Subjects included from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA) were women of European ancestry aged 18 years or older with a pathogenic variant in *BRCA1*. The majority of the participants were sampled through cancer genetics clinics. Multiple members of the same families were included in some instances. Fifty-eight studies from 24 countries contributed Oncoarray genotype data. After quality control (see below) and removal of overlapping participants with the BCAC OncoArray study, data were available on 15,566 *BRCA1* mutation carriers, of whom 7,784 were affected with breast cancer (Supplementary Table 2). We also obtained iCOGS genotype data on 3,342 *BRCA1* mutation carriers (1,630 with breast cancer) from 54 studies through CIMBA. All mutation carriers provided written informed consent and participated under ethically approved protocols.

OncoArray SNP selection

Approximately 50% of the SNPs for the OncoArray were selected as a “GWAS backbone” (Illumina HumanCore), which aimed to provide high coverage for the majority of common variants through imputation. The remaining allocation was selected from lists supplied by each of six disease-based consortia, together with a seventh lists of SNPs of interest to multiple disease groups. Approximately 72k SNPs were selected specifically for their relevance to breast cancer, based on prior evidence of association with overall or subtype-specific disease, with breast density or with breast tissue specific gene expression. Lists were merged, as described previously³⁴.

Genotype calling and quality control

Details of the genotype calling and quality control (QC) for the iCOGS and GWAS are described elsewhere^{19,20,23,30}, and those for OncoArray are described in the Supplementary Note.

Imputation

Genotypes for ~21M SNPs were imputed for all samples using the October 2014 (Phase 3) release of the 1000 Genomes Project data as the reference panel and Nhap=800. The iCOGS, OncoArray and six of the GWAS datasets were imputed using a two-stage imputation approach, using SHAPEIT⁷³ for phasing and IMPUTEv2⁷⁴ for imputation. The imputation was performed in 5Mb non-overlapping intervals. All subjects were split into subsets of ~10,000 samples, with subjects from the same grouped in the subset. The Breast and Prostate Cancer Cohort Consortium (BPC3) and Breast Cancer Family Registry (BCFR) GWAS performed the imputation separately using MACH and Minimac^{75,76}. We imputed genotypes for all SNPs that were polymorphic (MAF>0.1%) in either European or Asian samples. For the BCAC GWAS, data were included in the analysis for all SNPs with MAF>0.01 and imputation r^2 >0.3. For iCOGS and OncoArray we included data for all SNPs with imputation r^2 >0.3 and MAF>0.005.

Statistical analyses of BCAC data

Per-allele odds ratios and standard errors were generated for the Oncoarray, iCOGS and each GWAS, adjusting for principal components using logistic regression. The Oncoarray and iCOGS analyses were additionally adjusted for country and study, respectively. For the OncoArray dataset, principal components analysis was performed using data for 33,661 SNPs (which included the 2,318 markers of continental ancestry) with a MAF \geq 0.05 and maximum correlation of 0.1, using purpose-written software (PCcalc; see URLs section) to allow standard calculations to be performed sufficiently rapidly on a very large dataset. We used the first 10 principal components, as additional components did not further reduce inflation in the test statistics. We used nine principal components for the iCOGS and up to 10 principal components for the other GWAS, where this was found to reduce inflation.

OR estimates were derived using MACH for the BCFR GWAS, ProbABEL⁷⁷ for the BPC3 GWAS, SNPTEST (see URLs section) for the remaining GWAS and purpose written software for the iCOGS and Oncoarray datasets. OR estimates and standard errors were combined by a fixed effects inverse variance meta-analysis using METAL³⁹. This was first done across the eight GWAS, applying genomic control, as described previously²⁰. It was then applied (without genomic control) to combine findings from the three BCAC genotyping initiatives (GWAS, iCOGS, OncoArray).

The independence of signals from two variants at 11q22.3 was by fitting the logistic regression models described above with both variants as covariates. This was done separately for iCOGS and OncoArray data and results for each variant combined by meta-analysis.

For selected SNPs we estimated per-allele ORs by ER-status using all available BCAC data for 82,263 cases with known ER status and 87,962 controls from the iCOGS and OncoArray studies. We also estimated the per-allele ORs by TN status (TN versus other ER-negative subtypes) and tumour grade, using available BCAC data for ER-negative cases and corresponding controls. Tests for heterogeneity by

subtype were derived by applying logistic regression to cases only. This was done separately for the iCOGS and Oncoarray datasets, adjusted as before, and then combined in a fixed-effects meta-analysis. Multinomial regression was applied to cases only to test a linear trend for grade, with the model constrained so that the difference between grade 1 and 3 was double that for the difference between grade 2 and 3; this method was also used to test for a linear trend with age with ordinal values 1, 2, 3 and 4 representing ages <40, 40-49, 50-59 and ≥60, respectively.

Statistical analyses of CIMBA data

Associations between genotypes and breast cancer risk for *BRCA1* mutation carriers were evaluated using a 1 *df* per allele trend-test (*P*-trend), based on modeling the retrospective likelihood of the observed genotypes conditional on breast cancer phenotypes³⁶. This was done separately for iCOGS and OncoArray data. To allow for the non-independence among related individuals, an adjusted test statistic was used which took into account the correlation in genotypes³. All analyses were stratified by country of residence and, for countries where strata were sufficiently large (USA and Canada), by Ashkenazi Jewish ancestry. The results from the iCOGS and OncoArray datasets were then pooled using fixed effects meta-analysis. We repeated these analyses modelling ovarian cancer as a competing risk and observed no substantial difference in the results obtained.

The independence of signals from two variants at 11q22.3 was assessed using OncoArray data only, fitting a Cox regression model with per-allele effects for both variants, adjusting for birth cohort, stratified by country of residence and using robust standard errors and clustered observations for relatives. This approach provides valid significance tests of associations, although the HR estimates can be biased³⁵.

Meta-analysis of BCAC and CIMBA

A fixed effects meta-analysis of results from BCAC and CIMBA was conducted using an inverse variance approach assuming fixed effects, as implemented in METAL³⁹. The effect estimates used were the logarithm of the per-allele hazard ratio (HR) estimate for the association with breast cancer risk in *BRCA1* mutation carriers from CIMBA and the logarithm of the per-allele OR estimate for the association with risk of ER-negative breast cancer based on BCAC data, both of which were assumed to approximate the same relative risk. We assessed genomic inflation using common (MAF>1%) GWAS backbone variants. As lambda is influenced by sample size, we calculated lambda1000 to be comparable with other studies.

All statistical tests conducted were two-sided.

Definition of known hits

We identified all associations previously reported from genome-wide or candidate analysis at a significance level $P < 5 \times 10^{-8}$ for overall breast cancer, ER-negative or ER-positive breast cancer, in *BRCA1* or *BRCA2* carriers, or in meta-analyses of these categories. We included only one SNP in any 500kb interval, unless joint analysis provided genome-wide significant evidence (conditional $P < 5 \times 10^{-8}$) of more than one independent signal. Where multiple studies reported associations in the same region, we considered the first reported association unless a later study identified a different variant in the same region that was more strongly associated with breast cancer risk. One hundred and seven previously reported hits were

identified, 11 of these through GWAS of ER-negative disease or of breast cancer in *BRCA1* mutation carriers, or reported as more strongly associated with ER-negative breast cancer. These are listed in Table 2. The other 96 previously reported hits are listed in Supplementary Table 10.

Definition of new hits

To search for novel loci, we assessed all SNPs excluding those within 500kb of a known hit. This identified 206 SNPs in nine regions that were associated with disease risk at $P < 5 \times 10^{-8}$ in the meta-analysis of BCAC ER-negative breast cancer and CIMBA *BRCA1* mutation carriers. The SNP with lowest p-value from this analysis was considered the lead SNP. No additional loci were detected from the analysis of BCAC data only. Imputation quality, as assessed by the IMPUTE2 imputation r^2 in the Oncoarray dataset, was ≥ 0.89 for the 10 lead SNPs reported (Supplementary Table 3).

Candidate causal SNPs

To define the set of potentially causal variants at each of the novel susceptibility loci, we selected all variants with p-values within two orders of magnitude of the most significant SNP at each of the 10 novel loci. This is approximately equivalent to selecting variants whose posterior probability of causality is within two orders of magnitude of the most significant SNP^{40,41}. This approach was applied to identify potentially causal variants for the signal given by the more frequent lead SNP at 11q22.3 (rs11374964). A similar approach was applied for the rarer lead SNP at this locus (rs74911261), but based on p-values from analyses adjusted for rs11374964.

Proportion of familial risk explained

The relative risk of ER-negative breast cancer for the first degree female relative of a woman with ER-negative disease has not been estimated. We therefore assumed that the 2-fold risk observed for overall disease also applied to ER-negative disease. In order to estimate the proportion of this explained by the 125 variants associated with ER-negative disease, we used minor allele frequency and OR estimates from the OncoArray-based genotype data and applied the formula:

$\sum_i p_i(1 - p_i)(\beta_i^2 - \tau_i^2)/\ln(\lambda)$, where p_i is the minor allele frequency for variant i , β_i is the log(OR) estimate for variant i , τ_i is the standard error of β_i and $\lambda=2$ is the assumed overall familial relative risk.

The corresponding estimate for the FRR due to all variants is the *frailty scale* heritability, defined as $h_f^2 = \sum_i 2p_i(1 - p_i)\gamma_i^2$, where the sum over all variants and γ_i is the true relative risk conferred by variant i , assuming a log-additive model. We first obtained the estimated heritability based on the full set of summary estimates using LD Score Regression⁶⁸, which derives a heritability estimate on the observed scale. We then converted this to an estimate on the frailty scale using the formula $h_f^2 = h_{obs}^2 / P(1 - P)$, where P is the proportion of samples in the population that are cases.

Proportion of polygenic risk-modifying variance explained for *BRCA1* carriers.

The proportion of the variance in the polygenic frailty modifying risk in *BRCA1* carriers explained by the set of associated SNPs was estimated by $\sum_i \ln c_i / \sigma^2$, where

c_i is the squared estimated coefficient of variation in incidences associated with SNP_{*i*}⁷⁸ and σ^2 is the total polygenic variance, estimated from segregation data⁷⁹.

In Silico Annotation of Candidate Causal variants

We combined multiple sources of *in silico* functional annotation from public databases to help identify potential functional SNPs and target genes, based on previous observations that breast cancer susceptibility alleles are enriched in *cis*-regulatory elements and alter transcriptional activity^{28,80-82}. The influence of candidate causal variants on transcription factor binding sites was determined using the ENCODE-Motifs resource⁴³. To investigate functional elements enriched across the region encompassing the strongest candidate causal SNPs, we analysed chromatin biofeatures data from the Encyclopedia of DNA Elements (ENCODE) Project⁴², Roadmap Epigenomics Projects⁴⁴ and other data obtained through the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO) namely: Chromatin State Segmentation by Hidden Markov Models (chromHMM), DNase I hypersensitive and histone modifications of epigenetic markers H3K4, H3K9, and H3K27 in Human Mammary Epithelial (HMEC) and myoepithelial (MYO) cells, T47D and MCF7 breast cancer cells and transcription factor ChIP-seq in a range of breast cell lines (Supplementary Table 6). To identify the SNPs most likely to be functional we used RegulomeDB⁴⁵, and to identify putative target genes, we examined potential functional chromatin interactions between distal and proximal regulatory transcription-factor binding sites and the promoters at the risk regions, using Hi-C data generated in HMECs⁴⁷ and Chromatin Interaction Analysis by Paired End Tag (ChIA-PET) in MCF7 cells. This detects genome-wide interactions brought about by, or associated with, CCCTC-binding factor (CTCF), DNA polymerase II (POL2), and Estrogen Receptor (ER), all involved in transcriptional regulation⁴⁷. Annotation of putative *cis*-regulatory regions and predicted target genes used the Integrated Method for Predicting Enhancer Targets (IM-PET)⁴⁶, the “Predicting Specific Tissue Interactions of Genes and Enhancers” (PreSTIGE) algorithm⁴⁸, Hnisz⁵¹ and FANTOM⁴⁹. Intersections between candidate causal variants and regulatory elements were identified using Galaxy, BedTools v2.24 and HaploReg v4.1, and visualised in the UCSC Genome Browser. Publically available eQTL databases including Gene-Tissue Expression (GTEx,⁵⁰ version 6, multiple tissues) and Westra⁵² (blood), were queried for candidate causal variants.

eQTL analyses

Expression quantitative trait loci (eQTL) analyses were performed using data from The Cancer Genome Atlas (TCGA) and Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) projects^{59,60}.

The TCGA eQTL analysis was based on 79 ER-negative breast tumors that had matched gene expression, copy number, and methylation profiles together with the corresponding germline genotypes available. All 79 individuals were of European ancestry as ascertained using the genotype data and the Local Ancestry in admixed Populations (LAMP) software package (LAMP estimate cut-off >95% European)⁸³. Germline genotypes were imputed into the 1000 Genomes reference panel (October 2014 release) using IMPUTE2^{75,84}. Gene expression had been measured on the Illumina HiSeq 2000 RNA-Seq platform (gene-level RSEM normalized counts⁸⁵), copy number estimates were derived from the Affymetrix SNP 6.0 (somatic copy

number alteration minus germline copy number variation called using the GISTIC2 algorithm⁸⁶), and methylation beta values measured on the Illumina Infinium HumanMethylation450, as previously described⁵⁹. Primary TCGA eQTL analysis focused on all potentially causal variants in the 10 new regions associated with breast cancer risk in the meta-analysis of ER-negative cases and controls from BCAC and *BRCA1* mutation carriers from CIMBA. We considered all genes located up to 1 Mb on either side of each of these variants. The effects of tumor copy number and methylation on gene expression were first removed using a method described previously⁵⁸, and eQTL analysis was performed by linear regression as implemented in the R package Matrix eQTL⁸⁷.

The METABRIC eQTL analysis was based on 135 normal breast tissue samples resected from breast cancer patients of European ancestry. Germline genotyping for the METABRIC study was also done on the Affymetrix SNP 6.0, and ancestry estimation and imputation for this data set was conducted as described for TCGA. Gene expression in the METABRIC study had been measured using the Illumina HT12 microarray platform and we used probe-level estimates. As for TCGA, we considered all genes in 10 regions using Matrix eQTL.

We also performed additional eQTL analyses using the METABRIC data set for all variants within 1 Mb of *L3MBTL3* and *CDH2* and the expression of these specific genes.

Global Genomic Enrichment Analyses

We performed stratified LD score regression analyses⁶⁸ for ER- breast cancer using the summary statistics based on the meta-analyses of OncoArray, GWAS, iCOGS and CIMBA. We used all SNPs in the 1000 Genomes Project phase 1 v3 release that had a minor allele frequency > 1% and an imputation quality score $R^2 > 0.3$ in the OncoArray data. LD scores were calculated using the 1000 Genomes Project Phase 1 v3 EUR panel. Further details are provided in the Supplementary Note.

We tested the differences in functional enrichment between ER-positive and ER-negative subsets for individual features through a Wald test, using the regression coefficients and standard errors for the two subsets based on the models described above. Finally, we assessed the heritability due to genotyped and imputed SNPs⁷⁰ and estimated the genetic correlation between ER-positive and ER-negative breast cancer⁶⁹. The genetic correlation analysis was restricted to the ~1M SNPs included in HapMap 3.

Pathway Enrichment Analyses (see also the Supplementary Note)

The pathway gene set database

Human_GOBP_AllPathways_no_GO_iea_January_19_2016_symbol.gmt (GeneSets; see URLs section)⁶¹, was used for all analyses. Pathway size was determined by the total number of genes in the pathway to which SNPs in the imputed GWAS dataset could be mapped. To provide more biologically meaningful results, and reduce false positives, only pathways that contained between 10 and 200 genes were considered.

SNPs were mapped to the nearest gene within 500kb; those that were further than 500 kb away from any gene were excluded. Gene significance was calculated by

assigning the lowest p-value observed across all SNPs assigned to a gene^{63,64}, based on the meta-analysis of BCAC and CIMBA data described above.

The gene set enrichment analysis (GSEA)⁶¹ algorithm, as implemented in the GenGen package (see URLs section)^{62,63} was used to perform pathway analysis. Briefly, the algorithm calculates an enrichment score (ES) for each pathway based on a weighted Kolmogorov-Smirnov statistic⁶². Pathways that have most of their genes at the top of the ranked list of genes obtain higher ES values.

We defined an ES threshold ($ES \geq 0.41$) to yield a true-positive rate (TPR) of 0.20 and a false-positive rate (FPR) of 0.14, with true-positive pathways defined as those observed with false discovery rate (FDR) < 0.05 in a prior analysis carried out using the analytic approach defined above applied to iCOGS data for ER-negative disease.

To visualize the pathway enrichment analysis results, an enrichment map was created using the Enrichment Map (EM) v 2.1.0 app⁶¹ in Cytoscape v3.30⁸⁸, applying an edge-weighted force directed layout. To measure the contribution of each gene to enriched pathways and annotate the map, we reran the pathway enrichment analysis multiple times, each time excluding one gene. A gene was considered to drive the enrichment if the ES dropped to zero or less (pathway enrichment driver) after it was excluded. Pathways were grouped in the map if they shared >70% of their genes or their enrichment was driven by a shared gene.

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1077 CHA-PE1
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36A-PE1
JA-PE1_FAM181A1 MCF7 CHA-PE1
JA-PE1

36A-PE1
36A-PE1
36A-PE1
36A-PE1

1

35

IM-PE1_KDEL2 HMEC IM-PE1_C11a165 MCF7 CHA-PE1_KDEL2 MCF7 CHA-PE1_C11a165 HCC1954 IM-PE1

.LOG41923 GA: -0.0405219
.LOG41923 GA: -0.0405219

7CHA-PET

$\lambda = 0.0410264$
 $\gamma = 0.0320156, \text{CUAP1-C} = 0.0477839, \text{AL32-C} = 0.048936$
 $\lambda = 0.0293929$
 $\gamma = 0.0418833$

14MCF7-CHA-PET

$\lambda = 0.0207271$

Supplementary Table 4: Results for the two novel ER-negative susceptibility loci on 11q22.3

SNP	Chr	Position	Alleles [#]	BCAC ER-negative [†]			CIMBA <i>BRCA1</i> mutation carriers [‡]		
				MAF	OR (95%CI)	P-value	MAF	HR (95%CI)	P-value
Each SNP modelled individually									
rs11374964	11	108345515	G/GA	0.42	0.94 (0.92-0.96)	3.6x10 ⁻⁷	0.43	0.92 (0.89-0.95)	1.6x10 ⁻⁷
rs74911261	11	108357137	G/A	0.02	0.81 (0.74-0.89)	3.7x10 ⁻⁶	0.02	0.78 (0.70-0.87)	1.1x10 ⁻⁵
Both SNPs modelled together									
rs11374964	11	108345515	G/GA	0.42	0.95 (0.93-0.97)	3.5x10 ⁻⁵	0.43	0.93 (0.90-0.96)	5.1x10 ⁻⁶
rs74911261	11	108357137	G/A	0.02	0.84 (0.76-0.91)	8.6x10 ⁻⁵	0.02	0.81 (0.73-0.91)	3.3x10 ⁻⁴

[#]More common allele listed first, minor allele second; [†]Combined data from 16,988 ER-negative cases and 87,962 controls of European ancestry from the Breast Cancer Association Consortium (BCAC) - results differ from those in Table 1 as GWAS data were excluded (unit record data was not available to run the models with both SNPs together); [‡]Combined OncoArray data from 15,566 *BRCA1* mutation carriers from the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA), 7,784 of whom had developed breast cancer - estimates from multivariable Cox regression; Chr, chromosome; MAF, minor allele frequency; OR, odds ratio per copy of the minor allele; CI, confidence interval; HR, hazard ratio per copy of the minor allele

Supplementary Table 3: Ten novel loci associated with risk of estrogen receptor (ER)-negative breast cancer using meta-analysis of BCAC and CIMBA data, by genotyping initiative

[illegible]

chr2	151570136	1927729	CT	0.32	1.04	0.98(1.0)	1.86	0.1	0.69	0.97	1.08	1.12(1.1)	0.10	0.28	0.97	0.98	1.08	1.14(1.12)	2.81(0)	0.1	0.48	0.1	0.96	1.11	1.11(1.12)	5.00(0)	0.98	1.04	1.00(1.00)
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chr2; chromosome; More common allele listed first, minor allele frequency; MAF; minor allele frequency; r_{DIP} for between-study heterogeneity in the DRP [Ref. 1]; P-value for between-study heterogeneity in the OR; r_{GAS} for heterogeneity in the OR between genotyping initiatives (GWAS/COGS/OncArray); Phast.P-value for heterogeneity in the OR between genotyping initiatives (r_{Phast}^2) for between-country heterogeneity in the HR; Phast.P-value for between-country heterogeneity in the HR; r_{BCAC}^2 [imputation r²; BCAC (Breast Cancer Association Consortium) results based on GWAS data for 4,480 cases and 12,632 controls; COGS data for 7,333 cases and 42,468 controls and OncArray data 9,655 cases and 45,494 controls CIMBA (Consortium of Investigators of Modifiers of BRCA1/2) results were based on COGS data for 3,428BRCA1 carriers (1,630 with breast cancer) and OncArray data for 15,566BRCA2 mutation carriers (7,784 with breast cancer)]

Supplementary Table 2: CIMBA studies contributing data on *BRCA1* mutation carriers, by genotyping initiative

Acronym	Study Name	Country	OncoArray		iCOGS	
			Unaffected	Breast cancer	Unaffected	Breast cancer
BCFR-AU	Australian site of the Breast Cancer Family Registry	AUSTRALIA	13	25	0	2
BCFR-NC	Northern California site of the Breast Cancer Family Registry	USA	3	12	1	1
BCFR-NY	New York site of the Breast Cancer Family Registry	USA	24	37	4	5
BCFR-ON	Ontario site of the Breast Cancer Family Registry	CANADA	34	86	2	7
BCFR-PA	Philadelphia site of the Breast Cancer Family Registry	USA	26	17	14	16
BCFR-UT	Utah site of the Breast Cancer Family Registry	USA	135	64	1	0
BFBOCC	Baltic Familial Breast Ovarian Cancer Consortium	LITHUANIA/LATVIA	133	111	16	8
BIDMC	Beth Israel Deaconess Medical Center	USA	41	44	1	1
BMBSA	BRCA-gene mutations and breast cancer in South African women	SOUTH AFRICA	21	37	2	1
BRICOH	Beckman Research Institute of the City of Hope	USA	96	50	11	9
CBCS	Rigshospitalet	DENMARK	110	75	80	57
CNIO	Spanish National Cancer Centre	SPAIN	32	31	49	44
COH	City of Hope Cancer Center	USA	84	141	6	8
CONSIT TEAM	CONsorzio Studi Italiani sui Tumori Ereditari Alla Mammella	ITALY	265	271	217	234
DEMOKRITOS	National Centre for Scientific Research Demokritos	GREECE	85	132	12	20
DFCI	Dana-Farber Cancer Institute	USA	82	65	3	4
DKFZ	German Cancer Research Center	GERMANY	19	36	0	2
EMBRACE	Epidemiological Study of Familial Breast Cancer	UK/IRELAND	907	785	14	13
FCCC	Fox Chase Cancer Center	USA	49	26	20	19
FPGMX	Fundación Pública Galega de Medicina Xenómica	SPAIN	40	61		
GC-HBOC	German Familial Breast Group	GERMANY	673	1145	54	111
GEMO	Genetic Modifiers of cancer risk in BRCA1/2 mutation carriers	FRANCE/USA	630	842	114	111
GEORGETOWN	Georgetown University	USA	6	5	1	2
G-FAST	Ghent University Hospital	BELGIUM	69	121	91	42
HCSC	Hospital Clinico San Carlos	SPAIN	85	55	5	6
HEBCS	Helsinki Breast Cancer Study	FINLAND	67	53	3	5
HEBON	Genen Omgeving studie van de werkgroep Hereditair Borstkanker Onderzoek Nederland	NETHERLANDS	500	372	220	202
HUNBOCS	Molecular Genetic Studies of Breast- and Ovarian Cancer in Hungary	HUNGARY	101	179		
HVH	University Hospital Vall d'Hebron	SPAIN	56	62	0	1
ICO	Institut Català d'Oncologia	SPAIN	150	130	5	1
IHCC	International Hereditary Cancer Centre	POLAND	121	77	279	223
INHERIT	Interdisciplinary Health Research Internal Team BReast CAncer susceptibility	CANADA (QUEBEC)	52	37	6	2
IOVHBOCS	Istituto Oncologico Veneto	ITALY	93	111	5	4
IPOBCS	Portuguese Oncology Institute-Porto Breast Cancer Study	PORTUGAL	79	36	1	2
KCONFAB	Kathleen Cuningham Consortium for Research into Familial Breast Cancer	AUSTRALIA	355	366	24	26
KUMC	University of Kansas Medical Center	USA	3	11		
MAYO	Mayo Clinic	USA	126	121	12	10
MCGILL	McGill University	CANADA (QUEBEC)	30	24		
MODSQUAD	Modifier Study of Quantitative Effects on Disease	CZECH REPUBLIC			68	106
MSKCC	Memorial Sloane Kettering Cancer Center	USA	193	185	32	59
MUV	General Hospital Vienna	AUSTRIA	266	268	11	11
NAROD	Women's College Research Institute Hereditary Breast and Ovarian Cancer Study	CANADA			100	46
NCI	National Cancer Institute	USA	108	42	6	1
NNPIO	N.N. Petrov Institute of Oncology	RUSSIA	22	44	1	4
NORTHSHORE	NorthShore University HealthSystem	USA	40	40		
NRG_ONCOLOGY	NRG Oncology	USA/AUSTRALIA	153	166	4	7
OCGN	Ontario Cancer Genetics Network	CANADA	133	71	6	4
OSU CCG	The Ohio State University Comprehensive Cancer Center	USA	34	39	8	10
OUH	Odense University Hospital	DENMARK	358	192	10	10
PBCS	Università di Pisa	ITALY	39	49	6	5
SMC	Sheba Medical Centre	ISRAEL	99	65	57	41
SWE-BRCA	Swedish Breast Cancer Study	SWEDEN	237	188	52	38
UCHICAGO	University of Chicago	USA	51	43	7	0
UCSF	University of California San Francisco	USA	60	32	16	15
UKGRFOCR	UK and Gilda Radner Familial Ovarian Cancer Registries	UK	40	13	5	0
UPENN	University of Pennsylvania	USA	218	239	11	22
UPITT	Cancer Family Registry University of Pittsburg	USA	77	77		
UTMDACC	University of Texas MD Anderson Cancer Center	USA	18	25	27	45
VFCTG	Victorian Familial Cancer Trials Group	AUSTRALIA	104	103	2	1
WCP	Women's Cancer Program at Cedars-Sinai Medical Center	USA	137	50	10	6

Supplementary Table 1: BCAC studies contributing data on estrogen receptor negative cases and controls, by genotyping initiative †

Acronym	Study Name	Country	Study design	OncoArray		ICOGS		GWASs	
				Controls	Cases	Controls	Cases	Controls	Cases
ABCFS	Australian Breast Cancer Family Study	Australia	Case-control study	188	62				
ABCS	Amsterdam Breast Cancer Study	Netherlands	Case-control study	4	27	551	204	285	72
ABCTB	Australian Breast Cancer Tissue Bank	Australia	Case-control study	374	290	1815	154		
BBCC	Bavarian Breast Cancer Cases and Controls	Germany	Case-control study	248	354	458	67		
BBCS	British Breast Cancer Study	UK	Case-control study	442	18	1397	108		
BCEES	Breast Cancer Employment and Environment Study	Australia	Case-control study	834	115				
BCFR	Breast Cancer Family Registry	USA, Canada, Australia	Case-control study					2251	922
BCFR-NY	New York site of the Breast Cancer Family Registry	USA	Case-control study	27	60				
BCFR-PA	Philadelphia site of the Breast Cancer Family Registry	USA	Case-control study	0	27				
BCFR-UT	Utah site of the Breast Cancer Family Registry	USA	Case-control study	0	13				
BCINIS	Breast Cancer in Northern Israel Study	Israel	Case-control study	723	262				
BIGGS	Breast Cancer in Galway Genetic Study	Ireland	Case-control study			719	154		
BPC3	Breast and Prostate Cancer Cohort Consortium	International	Prospective cohorts: nested case-control studies					2305	1998
BREOGAN	Breast Oncology Galicia Network	Spain	Case-control study	725	246				
BSUCH	Breast Cancer Study of the University of Heidelberg	Germany	Case-control study	167	42	954	157		
CBCS	Canadian Breast Cancer Study	Canada	Case-control study	817	119				
CCGP	Crete Cancer Genetics Program	Greece	Case-control study	332	177				
CCOLE	CCOLE Breast Cancer Study	France	Case-control study	3	5	999	144		
CGPS	Copenhagen General Population Study	Denmark	Case-control study	712	160	4534	357		
CNIO-BCS	Spanish National Cancer Centre Breast Cancer Study	Spain	Case-control study			876	88		
CPsil	Cancer Prevention Study-II Nutrition Cohort	USA	Prospective cohort: nested case-control study	3025	99				
CTS	California Teachers Study	USA	Prospective cohort: nested case-control study	577	126	71	68		
DEMOKRITOS	Demokritos	Greece	Case-control study			95	413		
DIETCOMPLYF	DietComplyF Breast Cancer Survival Study	UK	Prospective cohort: nested case-control study	0	104				
EPIC	European Prospective Investigation Into Cancer and Nutrition	International (Europe)	Prospective cohort: nested case-control study	3522	179				
ESTHER	ESTHER Breast Cancer Study	Germany	Case-control study	3	1	502	98		
GC-HBOC*	German Consortium for Hereditary Breast & Ovarian Cancer	Germany	Case-control study	1593	358	168			
GENICA	Gene Environment Interaction and Breast Cancer in Germany	Germany	Case-control study	284	78	427	104		
GEPARSIXTO	Randomized phase II trial	Germany	Case-only study	0	273				
GESBC	Genetic Epidemiology Study of Breast Cancer by Age 50	Germany	Case-control study	180	122				
HABCS	Hannover Breast Cancer Study	Germany	Case-control study	865	147				
HCSC	Hospital Clinico San Carlos	Spain	Case-control study	0	109				
HEBCS	Helsinki Breast Cancer Study	Finland	Case-control study	2	14	1233	235	1012	145
HMBCS	Hannover-Minsk Breast Cancer Study	Belarus	Case-control study	214	7	130	8		
HUBCS	Hannover-Ufa Breast Cancer Study	Russia	Case-control study	131	18				
KARBAK	Karolinska Breast Cancer Study	Sweden	Case-control study	0	3	662	63		
KBCP	Kuopio Breast Cancer Project	Finland	Case-control study	182	23	250	97		
KConFab/AOCS	Kathleen Cunningham Foundation Consortium for research into Familial Breast Cancer/Australian Ovarian Cancer Study	Australia and New Zealand	Case-control study			897	55		
LMBC	Leuven Multidisciplinary Breast Centre	Belgium	Case-control study	435	145	1388	378		
MABCs	Macedonian Breast Cancer Study	Macedonia	Case-control study	93	17				
MARIE	Mammary Carcinoma Risk Factor Investigation	Germany	Case-control study	288	8	1778	346	470	76
MBCSG	Milan Breast Cancer Study Group	Italy	Case-control study	366	75	400	42		
MCBCS	Mayo Clinic Breast Cancer Study	USA	Case-control study	179	84	1931	269		
MCCS	Melbourne Collaborative Cohort Study	Australia	Prospective cohort: nested case-control study	712	77	511	110		
MEC	Multiethnic Cohort	USA	Prospective cohort: nested case-control study	127	3	741	87		
MISS	Melanoma Inquiry of Southern Sweder	Sweden	Prospective cohort: nested case-control study	1523	79				
MMHS	Mayo Mammography Health Study	USA	Prospective cohort: nested case-control study	1605	50				
MTLGEBCS	Montreal Gene-Environment Breast Cancer Study	Canada	Case-control study	29	2	436	64		
NBCS	Norwegian Breast Cancer Study	Norway	Case-control study			217	200		
NBHS	Nashville Breast Health Study	USA	Case-control study	613	163	118	125		
NC-BCFR	Northern California Breast Cancer Family Registry	USA	Case-control study	149	261				
NHS	Nurses Health Study	USA	Prospective cohort: nested case-control study	1804	203				
NHS2	Nurses Health Study 2	USA	Prospective cohort: nested case-control study	1905	224				
OBCS	Oulu Breast Cancer Study	Finland	Case-control study			414	100		
OFBCR	Ontario Familial Breast Cancer Registry	Canada	Case-control study	217	259	511	269		
ORIGO	Leiden University Medical Centre Breast Cancer Study	Netherlands	Prospective cohort: nested case-control study	660	230	327	70		
OSU	Ohio State University	USA	Case-control study			203	207		
PBCS	NCI Polish Breast Cancer Study	Poland	Case-control study	1658	547				
pKARMA	Karolinska Mammography Project for Risk Prediction of Breast Cancer - Case-Control Study	Sweden	Case-control study	6042	166	5568	701		
PLCO	The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial	USA	Prospective cohort: nested case-control study	858	184				
POSH	Prospective Study of Outcomes in Sporadic Versus Hereditary Breast Cancer	UK	Case-only study	0	207				
PREFACE	Evaluation of Predictive Factors regarding the Effectivity of Aromatase Inhibitor Therapy	Germany	Case-only study	0	15				
RBCS	Rotterdam Breast Cancer Study	Netherlands	Case-control study	231	87	699	124		
RPCI	Roswell Park Cancer Institute	USA	Case-control study			126	136		
SASBAC	Singapore and Sweden Breast Cancer Study	Sweden	Case-control study			661	43	756	109
SBCS	Sheffield Breast Cancer Study	UK	Case-control study			848	98		
SEARCH	Study of Epidemiology and Risk factors in Cancer Heredity	UK	Case-control study	989	420	8068	1173		
SISTER	The Sister Study	USA	Prospective cohort: nested case-control study	1560	282				
2SISTER	The Two Sister Study	USA	Case-only study	0	204				
SKKDKFZS*	Städtisches Klinikum Karlsruhe Deutsches Krebsforschungszentrum Study	Germany	Case-only study	0	298	0	135		
SMC	Swedish Mammography Cohort	Sweden	Prospective cohort: nested case-control study	708	195				
SUCCESSB	Simultaneous Study of Gemcitabine-Docetaxel Combination adjuvant treatment	Germany	Case-only study	0	159				
SUCCESSC	Simultaneous Study of Docetaxel Based Anthracycline Free Adjuvant Treatment Evaluation	Germany	Case-only study	0	204				
SZBCS	IHCC-Szczecin Breast Cancer Study	Poland	Case-control study	157	72	315	60		
TNBCC	Triple-Negative Breast Cancer Consortium	International	Case-control studies	0	288			2890	998
UCIBCS	UCI Breast Cancer Study	USA	Case-control study	258	73			2663	160
UK2	UK2 GWAS	UK	Case-control study						
UKBGs	UK Breakthrough Generations Study	UK	Prospective cohort: nested case-control study	567	78	470	22		
UKOPS	UK Ovarian Cancer Population Study	UK	Case-control study	974	0				
WHI	Women's Health Initiative	USA	Prospective cohort: nested case-control study	4613	658				

†Studies participated in one or more of the following genotyping initiatives: OncoArray, ICOGS or one of eight genome-wide association studies (GWASs)

*For the analysis of ICOGS data, cases from SKKDKFZS and controls from GC-HBOC included as one study

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In Silico Annotation of Candidate Causal Variants

Guide to results table (Supplementary Table 5) and UCSC Genome Browser session

Each candidate causal SNP has been annotated with publicly available genomic data in order to highlight potentially functional variants, prioritise experimental validation, and predict target genes. Annotations fall into categories relating to putative effects on transcription factors, regulatory element activities, expression quantitative trait loci (eQTL) and target gene prediction. For each variant, a link to the UCSC Genome Browser is provided that shows a 1 Mb region with relevant genomic data.

Transcription factors

Information regarding potential effects on transcription factor recognition sequences was obtained from the ENCODE-Motifs resource (<http://compbio.mit.edu/encode-motifs>)¹ using VCFtools v0.1.11 to access the downloaded HaploReg v4.0 database². The impact each variant has on the position weight matrix for specific transcription factors is expressed as '+' or '-' for strengthened or weakened motifs relative to elements carrying the reference allele, respectively. Processed transcription factor ChIP-seq peak data for breast cell types were downloaded from ENCODE and other publications via NCBI GEO, in BED or NarrowPeak format, converted to the hg19 assembly using LiftOver if required, and given a standardised naming system (format = "*celltype;target*" in Supplementary Table 5). More details about the overlapping binding sites may be found within browser session track "TF-chip peaks overlapping candidate SNP" where TF-ChIP-seq peaks are named in the format "*Biosample_term_name, Experiment_target, Biosample_treatments, Biological_replicate(s), File_accession*". All ChIP-seq datasets are listed in Supplementary Table 6. Variants were assessed for overlap with ChIP-seq peaks using BedTools v2.25.0³.

Regulatory features

Histone signatures derived from histone modification ChIP-seq experiments on breast cell types carried out by ENCODE, NIH Roadmap Epigenomics, and other published studies were obtained and formatted as for ChIP-seq data. Histone modification peaks overlapping candidate causal variants are represented as "*celltype;histone_mark*" in Supplementary Table 5 and "*Biosample_term_name, Experiment_target, Biosample_treatments, Biological_replicate(s), File_accession*" in the browser track "Histone modification ChIP-seq peaks overlapping candidate SNP". BedTools was used to intersect variants with histone signatures including commonly used marks associated with enhancers (H3K4me1, H3K4me2 and H3K27ac) and promoters (H3K4me3 and H3K9ac). Chromatin Hidden Markov Modelling (ChromHMM) states were obtained for breast cells from Roadmap (HMEC and myoepithelial cells) and published MCF7 data⁴ and filtered for states corresponding to 'enhancers' (Roadmap 25-state E13, E14, E15, E16, E17, E18) or 'promoters' (Roadmap 25-state E1, E2, E3, E4, E22, E23). Chromatin state features containing candidate variants are represented as "*celltype;chromatin_state*". Chromatin accessibility data obtained from ENCODE, Roadmap and other published sources via NCBI GEO measured using DNase-seq and FAIRE-seq for relevant breast cell types were also tested for overlap with candidate causal variants. Intersected regions are reported in the format "*celltype;method*". Scores based on RegulomeDB⁵ are presented for available SNPs (based on dbSNP141), where lower scores are increasingly likely to be functional (<http://regulomedb.org/help#score>).

eQTL

Genes showing expression levels correlated with query SNPs are shown in the column headed 'eQTL_target_all'. All genes reported to be associated with genotype in studies including GTEx version 6⁶ (expression in any GTEx tissue, P value cutoff 10^{-6}) and Westra *et al.*,⁷ (expression in whole blood). Genes associated with genotype in GTEx breast samples (N=186) are listed in the column "eQTL_GTEx.breast". eQTL data from TCGA and METABRIC studies for relevant variants are also presented (format "Associated_gene:EffectAllele:EffectDirection:P_value").

Other genomic features

Chromosomal position, the lead variant for the associated locus, and potentially conflicting rsIDs (assessed as overlapping at the query position) are given for each variant. GWAS tagSNPs were downloaded from the UCSC Table Browser (December 2015) and associated traits are listed if the tagSNP is within a 10 kb window of the candidate causal variant. NCBI RefSeq gene annotations were downloaded from the UCSC Table Browser and BedTools was used to determine overlapping genes ("Overlapping_RefGene"). The nearest RefGene transcription start site is also presented, given in the format "RefGeneTSS|distance". Basic genomic annotations such as intergenic, intronic, exonic, and untranslated regions based on RefSeq gene annotations were determined for each variant.

Target Gene Prediction

The column headed "Predicted_target_gene" lists genes predicted by various methods to be targets of, or the expression of which is associated with, regulatory elements in which the candidate causal variant lies. The reported gene is listed with cell type and method in the format "target:cell:method". A database was created comprising publicly available data based on various methods aiming to link enhancers with target genes (Annex to Supplementary Table 5). Laboratory based experimental approaches include genome-wide Chromatin Interaction Analysis with Paired-End-Tag sequencing (ChIA-PET)⁸, Hi-C⁹, and other Chromosome conformation capture (3C)-based techniques. Computational resources designed to predict target promoters by correlation of gene expression with ChIP-seq signals at specific regulatory elements including IM-PET¹⁰, PreSTIGE¹¹ and data from Hnisz *et al.*¹² are also included. These methods associate enhancers defined by histone modification ChIP-seq for H3K4me1 (PreSTIGE), H3K27ac (Hnisz), H3K4me1, H3K4me3 and H3K27ac (IM-PET) with gene expression signals measured by RNA-seq. FANTOM5¹³ data representing enhancer-promoter cap analysis of gene expression (CAGE) expression correlation from all cell types were downloaded from <http://enhancer.binf.ku.dk/>. Target genes have been predicted for multiple cell types and all data were included in the database, and filtered for breast derived cell types for this analysis (see Key to Supplementary Table 5).

The following strategy was used to assign potential target genes to regulatory elements. The published computational methods (Hnisz, PreSTIGE and IM-PET) included target gene annotation in the reported data. For ChIA-PET and Hi-C data, interaction peaks were mapped to promoters defined as -1.0 kb to +0.1 kb around GENCODE (v19) transcription start sites. Enhancer definitions were used as reported for computational methods while for ChIA-PET and Hi-C were interpreted as any region interacting with a promoter (regardless of other enhancer annotation information such as histone modification or open chromatin). FANTOM5 target promoters were predefined and

tissue specificity was determined by intersecting “TSS associated enhancers” with tissue-specific sets of enhancers.

All data were formatted to enable intersection of test variants with “enhancers” as defined by each method using the Galaxy “intersect” tool¹⁴. Each enhancer-promoter assignment or interaction was represented as a single record along with details about potential target promoter, cell type, method, scoring and confidence statistics from the original publication. A set of query SNPs (or any loci with genomic positional information in BED format) could be queried into a custom Galaxy workflow leading to generation of a table of predicted gene targets and a link to the UCSC Genome Browser for visualisation.

UCSC Genome Browser session

A custom session has been uploaded to UCSC Genome Browser¹⁵ to facilitate exploration of breast cancer risk associated variation and implicated regulatory features. This can be accessed via the hyperlink (ie. “browser”) in the functional annotation x/sx file. All standard Genome Browser data and functions are then available, including track display options (eg. right click on a particular track to activate visualisation options), highlighting regions (shift and mouse over region of interest), and the table browser (eg. to intersect or export data).

Within the session, Oncoarray candidate causal variants are shown in red, and names can be shown by activating “pack” mode (as for all tracks). Target gene prediction data from Hnisz, PreSTIGE and IM-PET shows enhancers depicted as black bars. The segment name revealed in ‘pack’ mode lists predicted target gene and cell-type (eg “WNT7B.MCF7”). ChIA-PET interactions, represented in BED12 format, have been filtered to remove duplicates and *trans*-chromosomal interactions. The interactions are shaded to reflect statistical confidence based on enrichment in the original experiment. ChIA-PET interaction names show the genomic co-ordinates of either-end of the interaction, the cell type (restricted to MCF7 for this analysis), the immunoprecipitation target, and the experimental replicate. Depicted interactions are restricted to those for which a candidate variant lies within an interaction “end” with the opposite end overlapping a TSS. All other interactions may be visualised by activating the standard ENCODE ChIA-PET track (\\Regulation\\ENCODE Chromatin Interactions Tracks\\ChIA-PET from ENCODE/GIS-Ruan).

Chromatin interactions based on *in situ* Hi-C data from HMEC cells were downloaded from NCBI GEO (accession GSE63525)⁹. Annotated loops (representing potential enhancer-promoter interactions) processed by HiCCUPS were reformatted as BED files and tested for overlap with RefSeq promoters to assign potential target genes. Opposing ends of TSS-overlap loops were then annotated as ‘potential enhancers’. Specific loop regions which overlap BC risk candidate causal variants are depicted as black segments and named “*TSS_target.Celltype*”.

Various classes of genomic data representing regulatory features which harbour candidate variants are shown as separate tracks:

- *Histone modification ChIP-seq peaks overlapping candidate SNP*
- *DNase HS and FAIRE-seq peaks overlapping candidate SNP*
- *TF-chip peaks overlapping candidate SNP*

As mentioned above, changing the track display to 'pack' mode will show details of the overlapping peak in the format:

"Biosample_term_name, Experiment_target, Biosample_treatments, Biological_replicate(s), File_accession".

A representation of all TF and histone ChIP-seq, DNase-seq, and FAIRE-seq data tested for overlap with candidate variants is shown in three histogram tracks (computed with BedTools genomeCoverageBed). These show the summed peak density at each genomic position and allow simple visualisation of loci with relative abundance of regulatory features.

Tracks for Roadmap Epigenomics Chromatin state models (based on imputed data - 25 state, 12 marks, 127 epigenomes) were generated for breast Myoepithelial and HMEC cells. Chromatin states were separated and colour coded for states related to enhancers, promoters, and transcribed regions.

The bottom track ("Oncoarray SNPs") shows all directly genotyped and imputed SNPs passing quality control (imputation $r^2 > 0.3$) as black ticks. SNPs from dbSNP build 138 with a MAF > 0.01 in European samples which were not informative are shown in red.

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OncoArray genotype calling and quality control

Of the 568,712 variants selected for genotyping on OncoArray, 533,631 were successfully manufactured on the array (including 778 duplicate probes). OncoArray genotyping of BCAC and CIMBA samples was conducted at six sites. Details of the genotyping calling for the OncoArray are described in more detail elsewhere¹⁶. Briefly, we developed a single calling pipeline that was applied to more than 500,000 samples. An initial cluster file was generated using from 56,284 samples, selected over all the major genotyping centres and ethnicities, using the Gentrain2 algorithm. Variants likely to have problematic clusters were selected for manual inspection using the following criteria: call rate below 99%, minor allele frequency (MAF) <0.001, poor Illumina intensity and clustering metrics, deviation from the MAF observed in the 1000 Genomes Project using the criterion: $\frac{(|p_1 - p_0| - 0.01)^2}{((p_1 + p_0)(2 - p_1 - p_0))} > C$, where p_0 and p_1 are the minor frequencies in the 1000 Genome Project and Oncoarray datasets, respectively, and $C=0.008$. (This latter criterion is approximately equivalent to excluding SNPs on the basis of a Chi-square statistic of 16 for the difference in allele frequencies, assuming 1,000 samples in each group). This resulted in manual adjustment of the cluster file for 3,964 variants, and the exclusion of 16,526 variants. The final cluster file was then applied to the full dataset.

We excluded SNPs with a call rate <95% in any consortium, not in Hardy-Weinberg equilibrium ($P < 10^{-7}$ in controls, or $P < 10^{-12}$ in cases) or with concordance <98% among 5,280 duplicate pairs. For the imputation, we additionally excluded SNPs with a MAF <1% and a call rate <98% in any consortium, SNPs that could not be linked to the 1000 Genomes Project reference, those with MAF for Europeans that differed from that for the 1000 Genomes Project and a further 1,128 SNPs where the cluster plot was judged to be not ideal. Of the 533,631 SNPs which were manufactured on the array, 494,763 passed the initial QC and 469,364 were used in the imputation (see below).

For BCAC, we excluded probable duplicate samples and close relatives within each study, and probable duplicates between studies. These were identified by identity by state (IBS) analysis using a set of approximately 38,000 uncorrelated ($r^2 < 0.1$) SNPs for OncoArray and iCOGS and 16,000 SNPs for GWAS. Based on inspection of the distribution of IBS values, we identified first-degree relative pairs using the criterion $0.82 < \text{IBS} < 0.90$ for OncoArray and $0.85 < \text{IBS} < 0.90$ for iCOGS; similar criteria were used for each GWAS (with limits depending on the IBS distribution in that study).

We applied LD score regression to the summary results from GWAS, iCOGS and OncoArray to assess the evidence of overlap in individuals between the three datasets. We conducted three pair-wise cross-trait regression analyses (GWAS-iCOGS, GWAS-OncoArray and iCOGS-OncoArray) and used the intercept from the regression analysis to estimate the amount of overlap¹⁷. Assuming that the phenotypic correlation is 1 (that is, a case is a case in all datasets and a control is a control in all datasets), we found that for GWAS-iCOGS, the estimated overlap was 1.5% of individuals, for GWAS-OncoArray, the estimated overlap was 3.8% of individuals, and for iCOGS-OncoArray, the estimated overlap was 0.2% of individuals. It is unlikely that this degree of overlap would have influenced the results obtained from our analyses.

We also excluded samples with a call rate <95% and samples with extreme heterozygosity (>4.9 standard deviations from the mean for the reported ethnicity). Ancestry analysis was performed using a standardized approach in which 2,318 ancestry informative markers with minor allele frequencies of 0.05 on a subset of ~66,000 samples including 505 Hapmap 2 samples. The contribution of each of the three major continental ancestry groups (European, Asian and African) was estimated by mapping each individual to regions of a triangle based on the first two principal components, as implemented in the software package FastPop (<http://sourceforge.net/projects/fastpop/>)¹⁸. Individuals were thus classified into 4 groups: European (defined as >80% European ancestry), East Asian (>40% Asian ancestry), African (>20% African ancestry) and other (not fulfilling any of the above criteria)¹⁶. Of the 152,492 samples genotyped, the final dataset consisted of 142,072 samples, of which 9,655 ER-negative cases and 45,494 controls of European origin had not been included in a previous GWAS and had not been genotyped using iCOGS and were included in this analysis.

For the CIMBA samples we excluded individuals of non-European ancestry using multi-dimensional scaling. For this purpose we selected 30,733 uncorrelated autosomal SNPs (pair-wise $r^2 < 0.10$) to compute the genomic kinship between all pairs of *BRCA1* and *BRCA2* carriers, along with 267 HapMap samples (CHB, JPT,

YRI and CEU). These were converted to distances and subjected to multidimensional scaling. Using the first two components, we calculated the proportion of European ancestry for each individual and excluded samples with >27% non-European ancestry to ensure that samples of Ashkenazi Jewish ancestry were included in the final sample.

Global Genomic Enrichment Analyses (further details)

We created a “full baseline model” as previously described¹⁹ that included 52 “baseline” genomic features (24 non-cell-type specific publicly available annotations, a 500-bp window around each of the 24 annotations and a 100-bp window around each of four ChIP-seq peaks) and one category containing all SNPs. We estimated the enrichment for these 53 functional categories in a single multivariable LD score regression analysis.

We subsequently performed analyses using cell-type specific annotations for the four histone marks H3K4me1, H3K4me3, H3K9ac and H3K27ac across 27-81 cell types, depending on histone mark, giving a total of 220 cell-type specific marks¹⁹. We estimated the enrichment for each of these marks after adjusting for the baseline annotations by running 220 LD score regressions, each adding a different histone mark to the baseline model. We observed no associations after adjusting for 220 tests

Pathway Enrichment Analyses (further details)

Pathway enrichment analysis was performed to identify pathways associated with ER-negative breast cancer risk, pointing to biological hypotheses that can be further tested experimentally.

The pathway gene set database used contains pathway gene sets from Reactome²⁰, NCI Pathway Interaction Database²¹, GO (Gene Ontology) biological process²², HumanCyc²³, MSigdb²⁴, NetPath²⁵ and Panther²⁶. GO pathways inferred from electronic annotation terms were excluded. Some manual annotation was performed on the pathway gene set database where annotation errors from public data were discovered. In particular, in several pathways, the PDPK1 gene was mistakenly entered as PDK1 gene and was manually corrected. The same pathway (e.g. apoptosis) may be defined in two or more databases with potentially different sets of genes, and all versions of these duplicate/overlapping pathways were included.

Gene information (hg19) was downloaded from the ANNOVAR²⁷ website (<http://www.openbioinformatics.org/annovar/>). Some pathways include genes that are also grouped closely together in the genome and are thus likely to share the significance of a single SNP, which would artificially increase the pathway significance in our analysis. This was the case for pathways including histone genes. Thus, we selected representative SNP-gene associations to control for this effect (chr6:26055031 for HIST1, chr1:120904839, 149864043 for HIST2, chr1: 228615251 for HIST3 and chr12: 14919727 for HIST4).

Although there are several methods for pathway enrichment analysis, we chose the GSEA approach as it is one of the most established methods that is threshold free; many other methods such as SRT, ALIGATOR and Plink set-based test require an arbitrary p-value threshold to be defined for SNPs and applied before pathway analysis.

To focus on pathway enrichment analysis results about which we were most confident, we implemented a number of filters. First, only pathways with positive ES and containing at least one gene linked to a significant SNP ($P < 5 \times 10^{-8}$) were retained for subsequent analysis. Second, we defined an ES threshold ($ES \geq 0.41$) based on a comparison with a gold standard pathway enrichment analysis we previously performed on the iCOGS data alone and where we were able to analytically compute FDR values by shuffling case/control labels (this was not computationally feasible with the more complex meta-analysis scheme used in this paper).

We chose the true positive rate (TPR) threshold by varying the TPR in steps of 0.1 and observing how the FPR changed. A TPR of 0.1 resulted in a very low FPR (0.02), but we considered this to be unduly conservative as it resulted in a small number of pathways (37, clustered into 8 themes) and excluded many pathways known to be involved in breast cancer. A TPR of 0.20 (FPR = 0.14) gave a reasonable balance between the true and false positive rates, while including pathways known to be involved in breast cancer. Thus this threshold was chosen for this study. A TPR of 0.3 gave an FPR of 0.30, which we considered high; further, the resulting additional pathways included (in addition to those included at TPR=0.2) were weaker (i.e. they had worse enrichment scores [$ES < 0.41$] and had relatively very few genes included) than pathways appearing at lower FPRs (and TPRs). We rejected TPR thresholds > 0.3 because each gave an FPR that was larger than the TPR.

Finally, we performed an in depth literature search on all resulting pathways to confirm their relevance to breast cancer biology, applying the following criteria: 1) reported in at least one of five published breast cancer pathway analyses²⁸⁻³²; or 2) reported elsewhere in the literature to be involved in breast cancer. We also removed pathways that were significant due to incorrect gene function annotation.

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In Silico Annotation of Candidate Causal Variants

Guide to results table (Supplementary Table 5) and UCSC Genome Browser session

Each candidate causal SNP has been annotated with publicly available genomic data in order to highlight potentially functional variants, prioritise experimental validation, and predict target genes. Annotations fall into categories relating to putative effects on transcription factors, regulatory element activities, expression quantitative trait loci (eQTL) and target gene prediction. For each variant, a link to the UCSC Genome Browser is provided that shows a 1 Mb region with relevant genomic data.

Transcription factors

Information regarding potential effects on transcription factor recognition sequences was obtained from the ENCODE-Motifs resource (<http://compbio.mit.edu/encode-motifs>)¹ using VCFtools v0.1.11 to access the downloaded HaploReg v4.0 database². The impact each variant has on the position weight matrix for specific transcription factors is expressed as '+' or '-' for strengthened or weakened motifs relative to elements carrying the reference allele, respectively. Processed transcription factor ChIP-seq peak data for breast cell types were downloaded from ENCODE and other publications via NCBI GEO, in BED or NarrowPeak format, converted to the hg19 assembly using LiftOver if required, and given a standardised naming system (format = "*celltype;target*" in Supplementary Table 5). More details about the overlapping binding sites may be found within browser session track "TF-chip peaks overlapping candidate SNP" where TF-ChIP-seq peaks are named in the format "*Biosample_term_name, Experiment_target, Biosample_treatments, Biological_replicate(s), File_accession*". All ChIP-seq datasets are listed in Supplementary Table 6. Variants were assessed for overlap with ChIP-seq peaks using BedTools v2.25.0³.

Regulatory features

Histone signatures derived from histone modification ChIP-seq experiments on breast cell types carried out by ENCODE, NIH Roadmap Epigenomics, and other published studies were obtained and formatted as for ChIP-seq data. Histone modification peaks overlapping candidate causal variants are represented as "*celltype;histone_mark*" in Supplementary Table 5 and "*Biosample_term_name, Experiment_target, Biosample_treatments, Biological_replicate(s), File_accession*" in the browser track "Histone modification ChIP-seq peaks overlapping candidate SNP". BedTools was used to intersect variants with histone signatures including commonly used marks associated with enhancers (H3K4me1, H3K4me2 and H3K27ac) and promoters (H3K4me3 and H3K9ac). Chromatin Hidden Markov Modelling (ChromHMM) states were obtained for breast cells from Roadmap (HMEC and myoepithelial cells) and published MCF7 data⁴ and filtered for states corresponding to 'enhancers' (Roadmap 25-state E13, E14, E15, E16, E17, E18) or 'promoters' (Roadmap 25-state E1, E2, E3, E4, E22, E23). Chromatin state features containing candidate variants are represented as "*celltype;chromatin_state*". Chromatin accessibility data obtained from ENCODE, Roadmap and other published sources via NCBI GEO measured using DNase-seq and FAIRE-seq for relevant breast cell types were also tested for overlap with candidate causal variants. Intersected regions are reported in the format "*celltype;method*". Scores based on RegulomeDB⁵ are presented for available SNPs (based on dbSNP141), where lower scores are increasingly likely to be functional (<http://regulomedb.org/help#score>).

eQTL

Genes showing expression levels correlated with query SNPs are shown in the column headed 'eQTL_target_all'. All genes reported to be associated with genotype in studies including GTEx version 6⁶ (expression in any GTEx tissue, P value cutoff 10^{-6}) and Westra *et al.*,⁷ (expression in whole blood). Genes associated with genotype in GTEx breast samples (N=186) are listed in the column "eQTL_GTEx.breast". eQTL data from TCGA and METABRIC studies for relevant variants are also presented (format "Associated_gene:EffectAllele:EffectDirection:P_value").

Other genomic features

Chromosomal position, the lead variant for the associated locus, and potentially conflicting rsIDs (assessed as overlapping at the query position) are given for each variant. GWAS tagSNPs were downloaded from the UCSC Table Browser (December 2015) and associated traits are listed if the tagSNP is within a 10 kb window of the candidate causal variant. NCBI RefSeq gene annotations were downloaded from the UCSC Table Browser and BedTools was used to determine overlapping genes ("Overlapping_RefGene"). The nearest RefGene transcription start site is also presented, given in the format "RefGeneTSS|distance". Basic genomic annotations such as intergenic, intronic, exonic, and untranslated regions based on RefSeq gene annotations were determined for each variant.

Target Gene Prediction

The column headed "Predicted_target_gene" lists genes predicted by various methods to be targets of, or the expression of which is associated with, regulatory elements in which the candidate causal variant lies. The reported gene is listed with cell type and method in the format "target:cell:method". A database was created comprising publicly available data based on various methods aiming to link enhancers with target genes (Annex to Supplementary Table 5). Laboratory based experimental approaches include genome-wide Chromatin Interaction Analysis with Paired-End-Tag sequencing (ChIA-PET)⁸, Hi-C⁹, and other Chromosome conformation capture (3C)-based techniques. Computational resources designed to predict target promoters by correlation of gene expression with ChIP-seq signals at specific regulatory elements including IM-PET¹⁰, PreSTIGE¹¹ and data from Hnisz *et al.*¹² are also included. These methods associate enhancers defined by histone modification ChIP-seq for H3K4me1 (PreSTIGE), H3K27ac (Hnisz), H3K4me1, H3K4me3 and H3K27ac (IM-PET) with gene expression signals measured by RNA-seq. FANTOM5¹³ data representing enhancer-promoter cap analysis of gene expression (CAGE) expression correlation from all cell types were downloaded from <http://enhancer.binf.ku.dk/>. Target genes have been predicted for multiple cell types and all data were included in the database, and filtered for breast derived cell types for this analysis (see Key to Supplementary Table 5).

The following strategy was used to assign potential target genes to regulatory elements. The published computational methods (Hnisz, PreSTIGE and IM-PET) included target gene annotation in the reported data. For ChIA-PET and Hi-C data, interaction peaks were mapped to promoters defined as -1.0 kb to +0.1 kb around GENCODE (v19) transcription start sites. Enhancer definitions were used as reported for computational methods while for ChIA-PET and Hi-C were interpreted as any region interacting with a promoter (regardless of other enhancer annotation information such as histone modification or open chromatin). FANTOM5 target promoters were predefined and

tissue specificity was determined by intersecting “TSS associated enhancers” with tissue-specific sets of enhancers.

All data were formatted to enable intersection of test variants with “enhancers” as defined by each method using the Galaxy “intersect” tool¹⁴. Each enhancer-promoter assignment or interaction was represented as a single record along with details about potential target promoter, cell type, method, scoring and confidence statistics from the original publication. A set of query SNPs (or any loci with genomic positional information in BED format) could be queried into a custom Galaxy workflow leading to generation of a table of predicted gene targets and a link to the UCSC Genome Browser for visualisation.

UCSC Genome Browser session

A custom session has been uploaded to UCSC Genome Browser¹⁵ to facilitate exploration of breast cancer risk associated variation and implicated regulatory features. This can be accessed via the hyperlink (ie. “browser”) in the functional annotation x/sx file. All standard Genome Browser data and functions are then available, including track display options (eg. right click on a particular track to activate visualisation options), highlighting regions (shift and mouse over region of interest), and the table browser (eg. to intersect or export data).

Within the session, Oncoarray candidate causal variants are shown in red, and names can be shown by activating “pack” mode (as for all tracks). Target gene prediction data from Hnisz, PreSTIGE and IM-PET shows enhancers depicted as black bars. The segment name revealed in ‘pack’ mode lists predicted target gene and cell-type (eg “WNT7B.MCF7”). ChIA-PET interactions, represented in BED12 format, have been filtered to remove duplicates and *trans*-chromosomal interactions. The interactions are shaded to reflect statistical confidence based on enrichment in the original experiment. ChIA-PET interaction names show the genomic co-ordinates of either-end of the interaction, the cell type (restricted to MCF7 for this analysis), the immunoprecipitation target, and the experimental replicate. Depicted interactions are restricted to those for which a candidate variant lies within an interaction “end” with the opposite end overlapping a TSS. All other interactions may be visualised by activating the standard ENCODE ChIA-PET track (\\Regulation\\ENCODE Chromatin Interactions Tracks\\ChIA-PET from ENCODE/GIS-Ruan).

Chromatin interactions based on *in situ* Hi-C data from HMEC cells were downloaded from NCBI GEO (accession GSE63525)⁹. Annotated loops (representing potential enhancer-promoter interactions) processed by HiCCUPS were reformatted as BED files and tested for overlap with RefSeq promoters to assign potential target genes. Opposing ends of TSS-overlap loops were then annotated as ‘potential enhancers’. Specific loop regions which overlap BC risk candidate causal variants are depicted as black segments and named “*TSS_target.Celltype*”.

Various classes of genomic data representing regulatory features which harbour candidate variants are shown as separate tracks:

- *Histone modification ChIP-seq peaks overlapping candidate SNP*
- *DNase HS and FAIRE-seq peaks overlapping candidate SNP*
- *TF-chip peaks overlapping candidate SNP*

As mentioned above, changing the track display to 'pack' mode will show details of the overlapping peak in the format:

"Biosample_term_name, Experiment_target, Biosample_treatments, Biological_replicate(s), File_accession".

A representation of all TF and histone ChIP-seq, DNase-seq, and FAIRE-seq data tested for overlap with candidate variants is shown in three histogram tracks (computed with BedTools genomeCoverageBed). These show the summed peak density at each genomic position and allow simple visualisation of loci with relative abundance of regulatory features.

Tracks for Roadmap Epigenomics Chromatin state models (based on imputed data - 25 state, 12 marks, 127 epigenomes) were generated for breast Myoepithelial and HMEC cells. Chromatin states were separated and colour coded for states related to enhancers, promoters, and transcribed regions.

The bottom track ("Oncoarray SNPs") shows all directly genotyped and imputed SNPs passing quality control (imputation $r^2 > 0.3$) as black ticks. SNPs from dbSNP build 138 with a MAF > 0.01 in European samples which were not informative are shown in red.

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OncoArray genotype calling and quality control

Of the 568,712 variants selected for genotyping on OncoArray, 533,631 were successfully manufactured on the array (including 778 duplicate probes). OncoArray genotyping of BCAC and CIMBA samples was conducted at six sites. Details of the genotyping calling for the OncoArray are described in more detail elsewhere¹⁶. Briefly, we developed a single calling pipeline that was applied to more than 500,000 samples. An initial cluster file was generated using from 56,284 samples, selected over all the major genotyping centres and ethnicities, using the Gentrain2 algorithm. Variants likely to have problematic clusters were selected for manual inspection using the following criteria: call rate below 99%, minor allele frequency (MAF) <0.001, poor Illumina intensity and clustering metrics, deviation from the MAF observed in the 1000 Genomes Project using the criterion: $\frac{(|p_1 - p_0| - 0.01)^2}{((p_1 + p_0)(2 - p_1 - p_0))} > C$, where p_0 and p_1 are the minor frequencies in the 1000 Genome Project and Oncoarray datasets, respectively, and $C=0.008$. (This latter criterion is approximately equivalent to excluding SNPs on the basis of a Chi-square statistic of 16 for the difference in allele frequencies, assuming 1,000 samples in each group). This resulted in manual adjustment of the cluster file for 3,964 variants, and the exclusion of 16,526 variants. The final cluster file was then applied to the full dataset.

We excluded SNPs with a call rate <95% in any consortium, not in Hardy-Weinberg equilibrium ($P < 10^{-7}$ in controls, or $P < 10^{-12}$ in cases) or with concordance <98% among 5,280 duplicate pairs. For the imputation, we additionally excluded SNPs with a MAF <1% and a call rate <98% in any consortium, SNPs that could not be linked to the 1000 Genomes Project reference, those with MAF for Europeans that differed from that for the 1000 Genomes Project and a further 1,128 SNPs where the cluster plot was judged to be not ideal. Of the 533,631 SNPs which were manufactured on the array, 494,763 passed the initial QC and 469,364 were used in the imputation (see below).

For BCAC, we excluded probable duplicate samples and close relatives within each study, and probable duplicates between studies. These were identified by identity by state (IBS) analysis using a set of approximately 38,000 uncorrelated ($r^2 < 0.1$) SNPs for OncoArray and iCOGS and 16,000 SNPs for GWAS. Based on inspection of the distribution of IBS values, we identified first-degree relative pairs using the criterion $0.82 < \text{IBS} < 0.90$ for OncoArray and $0.85 < \text{IBS} < 0.90$ for iCOGS; similar criteria were used for each GWAS (with limits depending on the IBS distribution in that study).

We applied LD score regression to the summary results from GWAS, iCOGS and OncoArray to assess the evidence of overlap in individuals between the three datasets. We conducted three pair-wise cross-trait regression analyses (GWAS-iCOGS, GWAS-OncoArray and iCOGS-OncoArray) and used the intercept from the regression analysis to estimate the amount of overlap¹⁷. Assuming that the phenotypic correlation is 1 (that is, a case is a case in all datasets and a control is a control in all datasets), we found that for GWAS-iCOGS, the estimated overlap was 1.5% of individuals, for GWAS-OncoArray, the estimated overlap was 3.8% of individuals, and for iCOGS-OncoArray, the estimated overlap was 0.2% of individuals. It is unlikely that this degree of overlap would have influenced the results obtained from our analyses.

We also excluded samples with a call rate <95% and samples with extreme heterozygosity (>4.9 standard deviations from the mean for the reported ethnicity). Ancestry analysis was performed using a standardized approach in which 2,318 ancestry informative markers with minor allele frequencies of 0.05 on a subset of ~66,000 samples including 505 Hapmap 2 samples. The contribution of each of the three major continental ancestry groups (European, Asian and African) was estimated by mapping each individual to regions of a triangle based on the first two principal components, as implemented in the software package FastPop (<http://sourceforge.net/projects/fastpop/>)¹⁸. Individuals were thus classified into 4 groups: European (defined as >80% European ancestry), East Asian (>40% Asian ancestry), African (>20% African ancestry) and other (not fulfilling any of the above criteria)¹⁶. Of the 152,492 samples genotyped, the final dataset consisted of 142,072 samples, of which 9,655 ER-negative cases and 45,494 controls of European origin had not been included in a previous GWAS and had not been genotyped using iCOGS and were included in this analysis.

For the CIMBA samples we excluded individuals of non-European ancestry using multi-dimensional scaling. For this purpose we selected 30,733 uncorrelated autosomal SNPs (pair-wise $r^2 < 0.10$) to compute the genomic kinship between all pairs of *BRCA1* and *BRCA2* carriers, along with 267 HapMap samples (CHB, JPT,

YRI and CEU). These were converted to distances and subjected to multidimensional scaling. Using the first two components, we calculated the proportion of European ancestry for each individual and excluded samples with >27% non-European ancestry to ensure that samples of Ashkenazi Jewish ancestry were included in the final sample.

Global Genomic Enrichment Analyses (further details)

We created a “full baseline model” as previously described¹⁹ that included 52 “baseline” genomic features (24 non-cell-type specific publicly available annotations, a 500-bp window around each of the 24 annotations and a 100-bp window around each of four ChIP-seq peaks) and one category containing all SNPs. We estimated the enrichment for these 53 functional categories in a single multivariable LD score regression analysis.

We subsequently performed analyses using cell-type specific annotations for the four histone marks H3K4me1, H3K4me3, H3K9ac and H3K27ac across 27-81 cell types, depending on histone mark, giving a total of 220 cell-type specific marks¹⁹. We estimated the enrichment for each of these marks after adjusting for the baseline annotations by running 220 LD score regressions, each adding a different histone mark to the baseline model. We observed no associations after adjusting for 220 tests

Pathway Enrichment Analyses (further details)

Pathway enrichment analysis was performed to identify pathways associated with ER-negative breast cancer risk, pointing to biological hypotheses that can be further tested experimentally.

The pathway gene set database used contains pathway gene sets from Reactome²⁰, NCI Pathway Interaction Database²¹, GO (Gene Ontology) biological process²², HumanCyc²³, MSigdb²⁴, NetPath²⁵ and Panther²⁶. GO pathways inferred from electronic annotation terms were excluded. Some manual annotation was performed on the pathway gene set database where annotation errors from public data were discovered. In particular, in several pathways, the PDPK1 gene was mistakenly entered as PDK1 gene and was manually corrected. The same pathway (e.g. apoptosis) may be defined in two or more databases with potentially different sets of genes, and all versions of these duplicate/overlapping pathways were included.

Gene information (hg19) was downloaded from the ANNOVAR²⁷ website (<http://www.openbioinformatics.org/annovar/>). Some pathways include genes that are also grouped closely together in the genome and are thus likely to share the significance of a single SNP, which would artificially increase the pathway significance in our analysis. This was the case for pathways including histone genes. Thus, we selected representative SNP-gene associations to control for this effect (chr6:26055031 for HIST1, chr1:120904839, 149864043 for HIST2, chr1: 228615251 for HIST3 and chr12: 14919727 for HIST4).

Although there are several methods for pathway enrichment analysis, we chose the GSEA approach as it is one of the most established methods that is threshold free; many other methods such as SRT, ALIGATOR and Plink set-based test require an arbitrary p-value threshold to be defined for SNPs and applied before pathway analysis.

To focus on pathway enrichment analysis results about which we were most confident, we implemented a number of filters. First, only pathways with positive ES and containing at least one gene linked to a significant SNP ($P < 5 \times 10^{-8}$) were retained for subsequent analysis. Second, we defined an ES threshold ($ES \geq 0.41$) based on a comparison with a gold standard pathway enrichment analysis we previously performed on the iCOGS data alone and where we were able to analytically compute FDR values by shuffling case/control labels (this was not computationally feasible with the more complex meta-analysis scheme used in this paper).

We chose the true positive rate (TPR) threshold by varying the TPR in steps of 0.1 and observing how the FPR changed. A TPR of 0.1 resulted in a very low FPR (0.02), but we considered this to be unduly conservative as it resulted in a small number of pathways (37, clustered into 8 themes) and excluded many pathways known to be involved in breast cancer. A TPR of 0.20 (FPR = 0.14) gave a reasonable balance between the true and false positive rates, while including pathways known to be involved in breast cancer. Thus this threshold was chosen for this study. A TPR of 0.3 gave an FPR of 0.30, which we considered high; further, the resulting additional pathways included (in addition to those included at TPR=0.2) were weaker (i.e. they had worse enrichment scores [$ES < 0.41$] and had relatively very few genes included) than pathways appearing at lower FPRs (and TPRs). We rejected TPR thresholds > 0.3 because each gave an FPR that was larger than the TPR.

Finally, we performed an in depth literature search on all resulting pathways to confirm their relevance to breast cancer biology, applying the following criteria: 1) reported in at least one of five published breast cancer pathway analyses²⁸⁻³²; or 2) reported elsewhere in the literature to be involved in breast cancer. We also removed pathways that were significant due to incorrect gene function annotation.

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In Silico Annotation of Candidate Causal Variants

Guide to results table (Supplementary Table 5) and UCSC Genome Browser session

Each candidate causal SNP has been annotated with publicly available genomic data in order to highlight potentially functional variants, prioritise experimental validation, and predict target genes. Annotations fall into categories relating to putative effects on transcription factors, regulatory element activities, expression quantitative trait loci (eQTL) and target gene prediction. For each variant, a link to the UCSC Genome Browser is provided that shows a 1 Mb region with relevant genomic data.

Transcription factors

Information regarding potential effects on transcription factor recognition sequences was obtained from the ENCODE-Motifs resource (<http://compbio.mit.edu/encode-motifs>)¹ using VCFtools v0.1.11 to access the downloaded HaploReg v4.0 database². The impact each variant has on the position weight matrix for specific transcription factors is expressed as '+' or '-' for strengthened or weakened motifs relative to elements carrying the reference allele, respectively. Processed transcription factor ChIP-seq peak data for breast cell types were downloaded from ENCODE and other publications via NCBI GEO, in BED or NarrowPeak format, converted to the hg19 assembly using LiftOver if required, and given a standardised naming system (format = "*celltype;target*" in Supplementary Table 5). More details about the overlapping binding sites may be found within browser session track "TF-chip peaks overlapping candidate SNP" where TF-ChIP-seq peaks are named in the format "*Biosample_term_name, Experiment_target, Biosample_treatments, Biological_replicate(s), File_accession*". All ChIP-seq datasets are listed in Supplementary Table 6. Variants were assessed for overlap with ChIP-seq peaks using BedTools v2.25.0³.

Regulatory features

Histone signatures derived from histone modification ChIP-seq experiments on breast cell types carried out by ENCODE, NIH Roadmap Epigenomics, and other published studies were obtained and formatted as for ChIP-seq data. Histone modification peaks overlapping candidate causal variants are represented as "*celltype;histone_mark*" in Supplementary Table 5 and "*Biosample_term_name, Experiment_target, Biosample_treatments, Biological_replicate(s), File_accession*" in the browser track "Histone modification ChIP-seq peaks overlapping candidate SNP". BedTools was used to intersect variants with histone signatures including commonly used marks associated with enhancers (H3K4me1, H3K4me2 and H3K27ac) and promoters (H3K4me3 and H3K9ac). Chromatin Hidden Markov Modelling (ChromHMM) states were obtained for breast cells from Roadmap (HMEC and myoepithelial cells) and published MCF7 data⁴ and filtered for states corresponding to 'enhancers' (Roadmap 25-state E13, E14, E15, E16, E17, E18) or 'promoters' (Roadmap 25-state E1, E2, E3, E4, E22, E23). Chromatin state features containing candidate variants are represented as "*celltype;chromatin_state*". Chromatin accessibility data obtained from ENCODE, Roadmap and other published sources via NCBI GEO measured using DNase-seq and FAIRE-seq for relevant breast cell types were also tested for overlap with candidate causal variants. Intersected regions are reported in the format "*celltype;method*". Scores based on RegulomeDB⁵ are presented for available SNPs (based on dbSNP141), where lower scores are increasingly likely to be functional (<http://regulomedb.org/help#score>).

eQTL

Genes showing expression levels correlated with query SNPs are shown in the column headed 'eQTL_target_all'. All genes reported to be associated with genotype in studies including GTEx version 6⁶ (expression in any GTEx tissue, P value cutoff 10^{-6}) and Westra *et al.*,⁷ (expression in whole blood). Genes associated with genotype in GTEx breast samples (N=186) are listed in the column "eQTL_GTEx.breast". eQTL data from TCGA and METABRIC studies for relevant variants are also presented (format "Associated_gene:EffectAllele:EffectDirection:P_value").

Other genomic features

Chromosomal position, the lead variant for the associated locus, and potentially conflicting rsIDs (assessed as overlapping at the query position) are given for each variant. GWAS tagSNPs were downloaded from the UCSC Table Browser (December 2015) and associated traits are listed if the tagSNP is within a 10 kb window of the candidate causal variant. NCBI RefSeq gene annotations were downloaded from the UCSC Table Browser and BedTools was used to determine overlapping genes ("Overlapping_RefGene"). The nearest RefGene transcription start site is also presented, given in the format "RefGeneTSS|distance". Basic genomic annotations such as intergenic, intronic, exonic, and untranslated regions based on RefSeq gene annotations were determined for each variant.

Target Gene Prediction

The column headed "Predicted_target_gene" lists genes predicted by various methods to be targets of, or the expression of which is associated with, regulatory elements in which the candidate causal variant lies. The reported gene is listed with cell type and method in the format "target:cell:method". A database was created comprising publicly available data based on various methods aiming to link enhancers with target genes (Annex to Supplementary Table 5). Laboratory based experimental approaches include genome-wide Chromatin Interaction Analysis with Paired-End-Tag sequencing (ChIA-PET)⁸, Hi-C⁹, and other Chromosome conformation capture (3C)-based techniques. Computational resources designed to predict target promoters by correlation of gene expression with ChIP-seq signals at specific regulatory elements including IM-PET¹⁰, PreSTIGE¹¹ and data from Hnisz *et al.*¹² are also included. These methods associate enhancers defined by histone modification ChIP-seq for H3K4me1 (PreSTIGE), H3K27ac (Hnisz), H3K4me1, H3K4me3 and H3K27ac (IM-PET) with gene expression signals measured by RNA-seq. FANTOM5¹³ data representing enhancer-promoter cap analysis of gene expression (CAGE) expression correlation from all cell types were downloaded from <http://enhancer.binf.ku.dk/>. Target genes have been predicted for multiple cell types and all data were included in the database, and filtered for breast derived cell types for this analysis (see Key to Supplementary Table 5).

The following strategy was used to assign potential target genes to regulatory elements. The published computational methods (Hnisz, PreSTIGE and IM-PET) included target gene annotation in the reported data. For ChIA-PET and Hi-C data, interaction peaks were mapped to promoters defined as -1.0 kb to +0.1 kb around GENCODE (v19) transcription start sites. Enhancer definitions were used as reported for computational methods while for ChIA-PET and Hi-C were interpreted as any region interacting with a promoter (regardless of other enhancer annotation information such as histone modification or open chromatin). FANTOM5 target promoters were predefined and

tissue specificity was determined by intersecting “TSS associated enhancers” with tissue-specific sets of enhancers.

All data were formatted to enable intersection of test variants with “enhancers” as defined by each method using the Galaxy “intersect” tool¹⁴. Each enhancer-promoter assignment or interaction was represented as a single record along with details about potential target promoter, cell type, method, scoring and confidence statistics from the original publication. A set of query SNPs (or any loci with genomic positional information in BED format) could be queried into a custom Galaxy workflow leading to generation of a table of predicted gene targets and a link to the UCSC Genome Browser for visualisation.

UCSC Genome Browser session

A custom session has been uploaded to UCSC Genome Browser¹⁵ to facilitate exploration of breast cancer risk associated variation and implicated regulatory features. This can be accessed via the hyperlink (ie. “browser”) in the functional annotation x/sx file. All standard Genome Browser data and functions are then available, including track display options (eg. right click on a particular track to activate visualisation options), highlighting regions (shift and mouse over region of interest), and the table browser (eg. to intersect or export data).

Within the session, Oncoarray candidate causal variants are shown in red, and names can be shown by activating “pack” mode (as for all tracks). Target gene prediction data from Hnisz, PreSTIGE and IM-PET shows enhancers depicted as black bars. The segment name revealed in ‘pack’ mode lists predicted target gene and cell-type (eg “WNT7B.MCF7”). ChIA-PET interactions, represented in BED12 format, have been filtered to remove duplicates and *trans*-chromosomal interactions. The interactions are shaded to reflect statistical confidence based on enrichment in the original experiment. ChIA-PET interaction names show the genomic co-ordinates of either-end of the interaction, the cell type (restricted to MCF7 for this analysis), the immunoprecipitation target, and the experimental replicate. Depicted interactions are restricted to those for which a candidate variant lies within an interaction “end” with the opposite end overlapping a TSS. All other interactions may be visualised by activating the standard ENCODE ChIA-PET track (\\Regulation\\ENCODE Chromatin Interactions Tracks\\ChIA-PET from ENCODE/GIS-Ruan).

Chromatin interactions based on *in situ* Hi-C data from HMEC cells were downloaded from NCBI GEO (accession GSE63525)⁹. Annotated loops (representing potential enhancer-promoter interactions) processed by HiCCUPS were reformatted as BED files and tested for overlap with RefSeq promoters to assign potential target genes. Opposing ends of TSS-overlap loops were then annotated as ‘potential enhancers’. Specific loop regions which overlap BC risk candidate causal variants are depicted as black segments and named “*TSS_target.Celltype*”.

Various classes of genomic data representing regulatory features which harbour candidate variants are shown as separate tracks:

- *Histone modification ChIP-seq peaks overlapping candidate SNP*
- *DNase HS and FAIRE-seq peaks overlapping candidate SNP*
- *TF-chip peaks overlapping candidate SNP*

As mentioned above, changing the track display to 'pack' mode will show details of the overlapping peak in the format:

"Biosample_term_name, Experiment_target, Biosample_treatments, Biological_replicate(s), File_accession".

A representation of all TF and histone ChIP-seq, DNase-seq, and FAIRE-seq data tested for overlap with candidate variants is shown in three histogram tracks (computed with BedTools genomeCoverageBed). These show the summed peak density at each genomic position and allow simple visualisation of loci with relative abundance of regulatory features.

Tracks for Roadmap Epigenomics Chromatin state models (based on imputed data - 25 state, 12 marks, 127 epigenomes) were generated for breast Myoepithelial and HMEC cells. Chromatin states were separated and colour coded for states related to enhancers, promoters, and transcribed regions.

The bottom track ("Oncoarray SNPs") shows all directly genotyped and imputed SNPs passing quality control (imputation $r^2 > 0.3$) as black ticks. SNPs from dbSNP build 138 with a MAF > 0.01 in European samples which were not informative are shown in red.

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OncoArray genotype calling and quality control

Of the 568,712 variants selected for genotyping on OncoArray, 533,631 were successfully manufactured on the array (including 778 duplicate probes). OncoArray genotyping of BCAC and CIMBA samples was conducted at six sites. Details of the genotyping calling for the OncoArray are described in more detail elsewhere¹⁶. Briefly, we developed a single calling pipeline that was applied to more than 500,000 samples. An initial cluster file was generated using from 56,284 samples, selected over all the major genotyping centres and ethnicities, using the Gentrain2 algorithm. Variants likely to have problematic clusters were selected for manual inspection using the following criteria: call rate below 99%, minor allele frequency (MAF) <0.001, poor Illumina intensity and clustering metrics, deviation from the MAF observed in the 1000 Genomes Project using the criterion: $\frac{(|p_1 - p_0| - 0.01)^2}{((p_1 + p_0)(2 - p_1 - p_0))} > C$, where p_0 and p_1 are the minor frequencies in the 1000 Genome Project and Oncoarray datasets, respectively, and $C=0.008$. (This latter criterion is approximately equivalent to excluding SNPs on the basis of a Chi-square statistic of 16 for the difference in allele frequencies, assuming 1,000 samples in each group). This resulted in manual adjustment of the cluster file for 3,964 variants, and the exclusion of 16,526 variants. The final cluster file was then applied to the full dataset.

We excluded SNPs with a call rate <95% in any consortium, not in Hardy-Weinberg equilibrium ($P < 10^{-7}$ in controls, or $P < 10^{-12}$ in cases) or with concordance <98% among 5,280 duplicate pairs. For the imputation, we additionally excluded SNPs with a MAF <1% and a call rate <98% in any consortium, SNPs that could not be linked to the 1000 Genomes Project reference, those with MAF for Europeans that differed from that for the 1000 Genomes Project and a further 1,128 SNPs where the cluster plot was judged to be not ideal. Of the 533,631 SNPs which were manufactured on the array, 494,763 passed the initial QC and 469,364 were used in the imputation (see below).

For BCAC, we excluded probable duplicate samples and close relatives within each study, and probable duplicates between studies. These were identified by identity by state (IBS) analysis using a set of approximately 38,000 uncorrelated ($r^2 < 0.1$) SNPs for OncoArray and iCOGS and 16,000 SNPs for GWAS. Based on inspection of the distribution of IBS values, we identified first-degree relative pairs using the criterion $0.82 < \text{IBS} < 0.90$ for OncoArray and $0.85 < \text{IBS} < 0.90$ for iCOGS; similar criteria were used for each GWAS (with limits depending on the IBS distribution in that study).

We applied LD score regression to the summary results from GWAS, iCOGS and OncoArray to assess the evidence of overlap in individuals between the three datasets. We conducted three pair-wise cross-trait regression analyses (GWAS-iCOGS, GWAS-OncoArray and iCOGS-OncoArray) and used the intercept from the regression analysis to estimate the amount of overlap¹⁷. Assuming that the phenotypic correlation is 1 (that is, a case is a case in all datasets and a control is a control in all datasets), we found that for GWAS-iCOGS, the estimated overlap was 1.5% of individuals, for GWAS-OncoArray, the estimated overlap was 3.8% of individuals, and for iCOGS-OncoArray, the estimated overlap was 0.2% of individuals. It is unlikely that this degree of overlap would have influenced the results obtained from our analyses.

We also excluded samples with a call rate <95% and samples with extreme heterozygosity (>4.9 standard deviations from the mean for the reported ethnicity). Ancestry analysis was performed using a standardized approach in which 2,318 ancestry informative markers with minor allele frequencies of 0.05 on a subset of ~66,000 samples including 505 Hapmap 2 samples. The contribution of each of the three major continental ancestry groups (European, Asian and African) was estimated by mapping each individual to regions of a triangle based on the first two principal components, as implemented in the software package FastPop (<http://sourceforge.net/projects/fastpop/>)¹⁸. Individuals were thus classified into 4 groups: European (defined as >80% European ancestry), East Asian (>40% Asian ancestry), African (>20% African ancestry) and other (not fulfilling any of the above criteria)¹⁶. Of the 152,492 samples genotyped, the final dataset consisted of 142,072 samples, of which 9,655 ER-negative cases and 45,494 controls of European origin had not been included in a previous GWAS and had not been genotyped using iCOGS and were included in this analysis.

For the CIMBA samples we excluded individuals of non-European ancestry using multi-dimensional scaling. For this purpose we selected 30,733 uncorrelated autosomal SNPs (pair-wise $r^2 < 0.10$) to compute the genomic kinship between all pairs of *BRCA1* and *BRCA2* carriers, along with 267 HapMap samples (CHB, JPT,

YRI and CEU). These were converted to distances and subjected to multidimensional scaling. Using the first two components, we calculated the proportion of European ancestry for each individual and excluded samples with >27% non-European ancestry to ensure that samples of Ashkenazi Jewish ancestry were included in the final sample.

Global Genomic Enrichment Analyses (further details)

We created a “full baseline model” as previously described¹⁹ that included 52 “baseline” genomic features (24 non-cell-type specific publicly available annotations, a 500-bp window around each of the 24 annotations and a 100-bp window around each of four ChIP-seq peaks) and one category containing all SNPs. We estimated the enrichment for these 53 functional categories in a single multivariable LD score regression analysis.

We subsequently performed analyses using cell-type specific annotations for the four histone marks H3K4me1, H3K4me3, H3K9ac and H3K27ac across 27-81 cell types, depending on histone mark, giving a total of 220 cell-type specific marks¹⁹. We estimated the enrichment for each of these marks after adjusting for the baseline annotations by running 220 LD score regressions, each adding a different histone mark to the baseline model. We observed no associations after adjusting for 220 tests

Pathway Enrichment Analyses (further details)

Pathway enrichment analysis was performed to identify pathways associated with ER-negative breast cancer risk, pointing to biological hypotheses that can be further tested experimentally.

The pathway gene set database used contains pathway gene sets from Reactome²⁰, NCI Pathway Interaction Database²¹, GO (Gene Ontology) biological process²², HumanCyc²³, MSigdb²⁴, NetPath²⁵ and Panther²⁶. GO pathways inferred from electronic annotation terms were excluded. Some manual annotation was performed on the pathway gene set database where annotation errors from public data were discovered. In particular, in several pathways, the PDPK1 gene was mistakenly entered as PDK1 gene and was manually corrected. The same pathway (e.g. apoptosis) may be defined in two or more databases with potentially different sets of genes, and all versions of these duplicate/overlapping pathways were included.

Gene information (hg19) was downloaded from the ANNOVAR²⁷ website (<http://www.openbioinformatics.org/annovar/>). Some pathways include genes that are also grouped closely together in the genome and are thus likely to share the significance of a single SNP, which would artificially increase the pathway significance in our analysis. This was the case for pathways including histone genes. Thus, we selected representative SNP-gene associations to control for this effect (chr6:26055031 for HIST1, chr1:120904839, 149864043 for HIST2, chr1: 228615251 for HIST3 and chr12: 14919727 for HIST4).

Although there are several methods for pathway enrichment analysis, we chose the GSEA approach as it is one of the most established methods that is threshold free; many other methods such as SRT, ALIGATOR and Plink set-based test require an arbitrary p-value threshold to be defined for SNPs and applied before pathway analysis.

To focus on pathway enrichment analysis results about which we were most confident, we implemented a number of filters. First, only pathways with positive ES and containing at least one gene linked to a significant SNP ($P < 5 \times 10^{-8}$) were retained for subsequent analysis. Second, we defined an ES threshold ($ES \geq 0.41$) based on a comparison with a gold standard pathway enrichment analysis we previously performed on the iCOGS data alone and where we were able to analytically compute FDR values by shuffling case/control labels (this was not computationally feasible with the more complex meta-analysis scheme used in this paper).

We chose the true positive rate (TPR) threshold by varying the TPR in steps of 0.1 and observing how the FPR changed. A TPR of 0.1 resulted in a very low FPR (0.02), but we considered this to be unduly conservative as it resulted in a small number of pathways (37, clustered into 8 themes) and excluded many pathways known to be involved in breast cancer. A TPR of 0.20 (FPR = 0.14) gave a reasonable balance between the true and false positive rates, while including pathways known to be involved in breast cancer. Thus this threshold was chosen for this study. A TPR of 0.3 gave an FPR of 0.30, which we considered high; further, the resulting additional pathways included (in addition to those included at TPR=0.2) were weaker (i.e. they had worse enrichment scores [$ES < 0.41$] and had relatively very few genes included) than pathways appearing at lower FPRs (and TPRs). We rejected TPR thresholds > 0.3 because each gave an FPR that was larger than the TPR.

Finally, we performed an in depth literature search on all resulting pathways to confirm their relevance to breast cancer biology, applying the following criteria: 1) reported in at least one of five published breast cancer pathway analyses²⁸⁻³²; or 2) reported elsewhere in the literature to be involved in breast cancer. We also removed pathways that were significant due to incorrect gene function annotation.

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Supplementary Table 1: BCAC studies contributing data on estrogen receptor negative cases and controls, by genotyping initiative †

Acronym	Study Name	Country	Study design	OncoArray		ICOGS		GWASs	
				Controls	Cases	Controls	Cases	Controls	Cases
ABCFS	Australian Breast Cancer Family Study	Australia	Case-control study	188	62				
ABCS	Amsterdam Breast Cancer Study	Netherlands	Case-control study	4	27	551	204	285	72
ABCTB	Australian Breast Cancer Tissue Bank	Australia	Case-control study	374	290	1815	154		
BBCC	Bavarian Breast Cancer Cases and Controls	Germany	Case-control study	248	354	458	67		
BBCS	British Breast Cancer Study	UK	Case-control study	442	18	1397	108		
BCEES	Breast Cancer Employment and Environment Study	Australia	Case-control study	834	115				
BCFR	Breast Cancer Family Registry	USA, Canada, Australia	Case-control study					2251	922
BCFR-NY	New York site of the Breast Cancer Family Registry	USA	Case-control study	27	60				
BCFR-PA	Philadelphia site of the Breast Cancer Family Registry	USA	Case-control study	0	27				
BCFR-UT	Utah site of the Breast Cancer Family Registry	USA	Case-control study	0	13				
BCINIS	Breast Cancer in Northern Israel Study	Israel	Case-control study	723	262				
BIGGS	Breast Cancer in Galway Genetic Study	Ireland	Case-control study			719	154		
BPC3	Breast and Prostate Cancer Cohort Consortium	International	Prospective cohorts: nested case-control studies					2305	1998
BREOGAN	Breast Oncology Galicia Network	Spain	Case-control study	725	246				
BSUCH	Breast Cancer Study of the University of Heidelberg	Germany	Case-control study	167	42	954	157		
CBCS	Canadian Breast Cancer Study	Canada	Case-control study	817	119				
CCGP	Crete Cancer Genetics Program	Greece	Case-control study	332	177				
CCOLE	CCOLE Breast Cancer Study	France	Case-control study	3	5	999	144		
CGPS	Copenhagen General Population Study	Denmark	Case-control study	712	160	4534	357		
CNIO-BCS	Spanish National Cancer Centre Breast Cancer Study	Spain	Case-control study			876	88		
CPsil	Cancer Prevention Study-II Nutrition Cohort	USA	Prospective cohort: nested case-control study	3025	99				
CTS	California Teachers Study	USA	Prospective cohort: nested case-control study	577	126	71	68		
DEMOKRITOS	Demokritos	Greece	Case-control study			95	413		
DIETCOMPLYF	DietComplyF Breast Cancer Survival Study	UK	Prospective cohort: nested case-control study	0	104				
EPIC	European Prospective Investigation Into Cancer and Nutrition	International (Europe)	Prospective cohort: nested case-control study	3522	179				
ESTHER	ESTHER Breast Cancer Study	Germany	Case-control study	3	1	502	98		
GC-HBOC*	German Consortium for Hereditary Breast & Ovarian Cancer	Germany	Case-control study	1593	358	168			
GENICA	Gene Environment Interaction and Breast Cancer in Germany	Germany	Case-control study	284	78	427	104		
GEPARSIXTO	Randomized phase II trial	Germany	Case-only study	0	273				
GESBC	Genetic Epidemiology Study of Breast Cancer by Age 50	Germany	Case-control study	180	122				
HABCS	Hannover Breast Cancer Study	Germany	Case-control study	865	147				
HCSC	Hospital Clinico San Carlos	Spain	Case-control study	0	109				
HEBCS	Helsinki Breast Cancer Study	Finland	Case-control study	2	14	1233	235	1012	145
HMBCS	Hannover-Minsk Breast Cancer Study	Belarus	Case-control study	214	7	130	8		
HUBCS	Hannover-Ufa Breast Cancer Study	Russia	Case-control study	131	18				
KARBAK	Karolinska Breast Cancer Study	Sweden	Case-control study	0	3	662	63		
KBCP	Kuopio Breast Cancer Project	Finland	Case-control study	182	23	250	97		
KConFab/AOCS	Kathleen Cunningham Foundation Consortium for research into Familial Breast Cancer/Australian Ovarian Cancer Study	Australia and New Zealand	Case-control study			897	55		
LMBC	Leuven Multidisciplinary Breast Centre	Belgium	Case-control study	435	145	1388	378		
MABCs	Macedonian Breast Cancer Study	Macedonia	Case-control study	93	17				
MARIE	Mammary Carcinoma Risk Factor Investigation	Germany	Case-control study	288	8	1778	346	470	76
MBCSG	Milan Breast Cancer Study Group	Italy	Case-control study	366	75	400	42		
MCBCS	Mayo Clinic Breast Cancer Study	USA	Case-control study	179	84	1931	269		
MCCS	Melbourne Collaborative Cohort Study	Australia	Prospective cohort: nested case-control study	712	77	511	110		
MEC	Multiethnic Cohort	USA	Prospective cohort: nested case-control study	127	3	741	87		
MISS	Melanoma Inquiry of Southern Sweder	Sweden	Prospective cohort: nested case-control study	1523	79				
MMHS	Mayo Mammography Health Study	USA	Prospective cohort: nested case-control study	1605	50				
MTLGEBCS	Montreal Gene-Environment Breast Cancer Study	Canada	Case-control study	29	2	436	64		
NBCS	Norwegian Breast Cancer Study	Norway	Case-control study			217	200		
NBHS	Nashville Breast Health Study	USA	Case-control study	613	163	118	125		
NC-BCFR	Northern California Breast Cancer Family Registry	USA	Case-control study	149	261				
NHS	Nurses Health Study	USA	Prospective cohort: nested case-control study	1804	203				
NHS2	Nurses Health Study 2	USA	Prospective cohort: nested case-control study	1905	224				
OBCS	Oulu Breast Cancer Study	Finland	Case-control study			414	100		
OFBCR	Ontario Familial Breast Cancer Registry	Canada	Case-control study	217	259	511	269		
ORIGO	Leiden University Medical Centre Breast Cancer Study	Netherlands	Prospective cohort: nested case-control study	660	230	327	70		
OSU	Ohio State University	USA	Case-control study			203	207		
PBCS	NCI Polish Breast Cancer Study	Poland	Case-control study	1658	547				
pKARMA	Karolinska Mammography Project for Risk Prediction of Breast Cancer - Case-Control Study	Sweden	Case-control study	6042	166	5568	701		
PLCO	The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial	USA	Prospective cohort: nested case-control study	858	184				
POSH	Prospective Study of Outcomes in Sporadic Versus Hereditary Breast Cancer	UK	Case-only study	0	207				
PREFACE	Evaluation of Predictive Factors regarding the Effectivity of Aromatase Inhibitor Therapy	Germany	Case-only study	0	15				
RBCS	Rotterdam Breast Cancer Study	Netherlands	Case-control study	231	87	699	124		
RPCI	Roswell Park Cancer Institute	USA	Case-control study			126	136		
SASBAC	Singapore and Sweden Breast Cancer Study	Sweden	Case-control study			661	43	756	109
SBCS	Sheffield Breast Cancer Study	UK	Case-control study			848	98		
SEARCH	Study of Epidemiology and Risk factors in Cancer Heredity	UK	Case-control study	989	420	8068	1173		
SISTER	The Sister Study	USA	Prospective cohort: nested case-control study	1560	282				
2SISTER	The Two Sister Study	USA	Case-only study	0	204				
SKKDKFZS*	Städtisches Klinikum Karlsruhe Deutsches Krebsforschungszentrum Study	Germany	Case-only study	0	298	0	135		
SMC	Swedish Mammography Cohort	Sweden	Prospective cohort: nested case-control study	708	195				
SUCCESSB	Simultaneous Study of Gemcitabine-Docetaxel Combination adjuvant treatment	Germany	Case-only study	0	159				
SUCCESSC	Simultaneous Study of Docetaxel Based Anthracycline Free Adjuvant Treatment Evaluation	Germany	Case-only study	0	204				
SZBCS	IHCC-Szczecin Breast Cancer Study	Poland	Case-control study	157	72	315	60		
TNBCC	Triple-Negative Breast Cancer Consortium	International	Case-control studies	0	288			2890	998
UCIBCS	UCI Breast Cancer Study	USA	Case-control study	258	73			2663	160
UK2	UK2 GWAS	UK	Case-control study						
UKBGs	UK Breakthrough Generations Study	UK	Prospective cohort: nested case-control study	567	78	470	22		
UKOPS	UK Ovarian Cancer Population Study	UK	Case-control study	974	0				
WHI	Women's Health Initiative	USA	Prospective cohort: nested case-control study	4613	658				

†Studies participated in one or more of the following genotyping initiatives: OncoArray, ICOGS or one of eight genome-wide association studies (GWASs)

*For the analysis of ICOGS data, cases from SKKDKFZS and controls from GC-HBOC included as one study

Supplementary Table 2: CIMBA studies contributing data on *BRCA1* mutation carriers, by genotyping initiative

Acronym	Study Name	Country	OncoArray		iCOGS	
			Unaffected	Breast cancer	Unaffected	Breast cancer
BCFR-AU	Australian site of the Breast Cancer Family Registry	AUSTRALIA	13	25	0	2
BCFR-NC	Northern California site of the Breast Cancer Family Registry	USA	3	12	1	1
BCFR-NY	New York site of the Breast Cancer Family Registry	USA	24	37	4	5
BCFR-ON	Ontario site of the Breast Cancer Family Registry	CANADA	34	86	2	7
BCFR-PA	Philadelphia site of the Breast Cancer Family Registry	USA	26	17	14	16
BCFR-UT	Utah site of the Breast Cancer Family Registry	USA	135	64	1	0
BFBOCC	Baltic Familial Breast Ovarian Cancer Consortium	LITHUANIA/LATVIA	133	111	16	8
BIDMC	Beth Israel Deaconess Medical Center	USA	41	44	1	1
BMBSA	BRCA-gene mutations and breast cancer in South African women	SOUTH AFRICA	21	37	2	1
BRICOH	Beckman Research Institute of the City of Hope	USA	96	50	11	9
CBCS	Rigshospitalet	DENMARK	110	75	80	57
CNIO	Spanish National Cancer Centre	SPAIN	32	31	49	44
COH	City of Hope Cancer Center	USA	84	141	6	8
CONSIT TEAM	CONsorzio Studi Italiani sui Tumori Ereditari Alla Mammella	ITALY	265	271	217	234
DEMOKRITOS	National Centre for Scientific Research Demokritos	GREECE	85	132	12	20
DFCI	Dana-Farber Cancer Institute	USA	82	65	3	4
DKFZ	German Cancer Research Center	GERMANY	19	36	0	2
EMBRACE	Epidemiological Study of Familial Breast Cancer	UK/IRELAND	907	785	14	13
FCCC	Fox Chase Cancer Center	USA	49	26	20	19
FPGMX	Fundación Pública Galega de Medicina Xenómica	SPAIN	40	61		
GC-HBOC	German Familial Breast Group	GERMANY	673	1145	54	111
GEMO	Genetic Modifiers of cancer risk in BRCA1/2 mutation carriers	FRANCE/USA	630	842	114	111
GEORGETOWN	Georgetown University	USA	6	5	1	2
G-FAST	Ghent University Hospital	BELGIUM	69	121	91	42
HCSC	Hospital Clinico San Carlos	SPAIN	85	55	5	6
HEBCS	Helsinki Breast Cancer Study	FINLAND	67	53	3	5
HEBON	Genen Omgeving studie van de werkgroep Hereditair Borstkanker Onderzoek Nederland	NETHERLANDS	500	372	220	202
HUNBOCS	Molecular Genetic Studies of Breast- and Ovarian Cancer in Hungary	HUNGARY	101	179		
HVH	University Hospital Vall d'Hebron	SPAIN	56	62	0	1
ICO	Institut Català d'Oncologia	SPAIN	150	130	5	1
IHCC	International Hereditary Cancer Centre	POLAND	121	77	279	223
INHERIT	Interdisciplinary Health Research Internal Team BReast CAncer susceptibility	CANADA (QUEBEC)	52	37	6	2
IOVHBOCS	Istituto Oncologico Veneto	ITALY	93	111	5	4
IPOBCS	Portuguese Oncology Institute-Porto Breast Cancer Study	PORTUGAL	79	36	1	2
KCONFAB	Kathleen Cuningham Consortium for Research into Familial Breast Cancer	AUSTRALIA	355	366	24	26
KUMC	University of Kansas Medical Center	USA	3	11		
MAYO	Mayo Clinic	USA	126	121	12	10
MCGILL	McGill University	CANADA (QUEBEC)	30	24		
MODSQUAD	Modifier Study of Quantitative Effects on Disease	CZECH REPUBLIC			68	106
MSKCC	Memorial Sloane Kettering Cancer Center	USA	193	185	32	59
MUV	General Hospital Vienna	AUSTRIA	266	268	11	11
NAROD	Women's College Research Institute Hereditary Breast and Ovarian Cancer Study	CANADA			100	46
NCI	National Cancer Institute	USA	108	42	6	1
NNPIO	N.N. Petrov Institute of Oncology	RUSSIA	22	44	1	4
NORTHSHORE	NorthShore University HealthSystem	USA	40	40		
NRG_ONCOLOGY	NRG Oncology	USA/AUSTRALIA	153	166	4	7
OCGN	Ontario Cancer Genetics Network	CANADA	133	71	6	4
OSU CCG	The Ohio State University Comprehensive Cancer Center	USA	34	39	8	10
OUH	Odense University Hospital	DENMARK	358	192	10	10
PBCS	Università di Pisa	ITALY	39	49	6	5
SMC	Sheba Medical Centre	ISRAEL	99	65	57	41
SWE-BRCA	Swedish Breast Cancer Study	SWEDEN	237	188	52	38
UCHICAGO	University of Chicago	USA	51	43	7	0
UCSF	University of California San Francisco	USA	60	32	16	15
UKGRFOCR	UK and Gilda Radner Familial Ovarian Cancer Registries	UK	40	13	5	0
UPENN	University of Pennsylvania	USA	218	239	11	22
UPITT	Cancer Family Registry University of Pittsburg	USA	77	77		
UTMDACC	University of Texas MD Anderson Cancer Center	USA	18	25	27	45
VFTG	Victorian Familial Cancer Trials Group	AUSTRALIA	104	103	2	1
WCP	Women's Cancer Program at Cedars-Sinai Medical Center	USA	137	50	10	6

Supplementary Table 3: Ten novel loci associated with risk of estrogen receptor (ER)-negative breast cancer using meta-analysis of BCAC and CIMBA data, by genotyping initiative

[illegible][illegible]

Supplementary Table 4: Results for the two novel ER-negative susceptibility loci on 11q22.3

SNP	Chr	Position	Alleles [#]	BCAC ER-negative [†]			CIMBA <i>BRCA1</i> mutation carriers [‡]		
				MAF	OR (95%CI)	P-value	MAF	HR (95%CI)	P-value
Each SNP modelled individually									
rs11374964	11	108345515	G/GA	0.42	0.94 (0.92-0.96)	3.6x10 ⁻⁷	0.43	0.92 (0.89-0.95)	1.6x10 ⁻⁷
rs74911261	11	108357137	G/A	0.02	0.81 (0.74-0.89)	3.7x10 ⁻⁶	0.02	0.78 (0.70-0.87)	1.1x10 ⁻⁵
Both SNPs modelled together									
rs11374964	11	108345515	G/GA	0.42	0.95 (0.93-0.97)	3.5x10 ⁻⁵	0.43	0.93 (0.90-0.96)	5.1x10 ⁻⁶
rs74911261	11	108357137	G/A	0.02	0.84 (0.76-0.91)	8.6x10 ⁻⁵	0.02	0.81 (0.73-0.91)	3.3x10 ⁻⁴

[#]More common allele listed first, minor allele second; [†]Combined data from 16,988 ER-negative cases and 87,962 controls of European ancestry from the Breast Cancer Association Consortium (BCAC) - results differ from those in Table 1 as GWAS data were excluded (unit record data was not available to run the models with both SNPs together); [‡]Combined OncoArray data from 15,566 *BRCA1* mutation carriers from the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA), 7,784 of whom had developed breast cancer - estimates from multivariable Cox regression; Chr, chromosome; MAF, minor allele frequency; OR, odds ratio per copy of the minor allele; CI, confidence interval; HR, hazard ratio per copy of the minor allele

[illegible]

166
APE
166
166

1077CHA-PE1
1077CHA-PE1
1077CHA-PE1
1077CHA-PE1
1077CHA-PE1
1077CHA-PE1

1.1MCF7CHA-PET
1.1MCF7CHA-PET

36A-PET
JA-PET_FAM1811MCF7CHA-PE1
JA-PET

36A-PET
36A-PET
36A-PET
36A-PET

1

35

IM-PET_KDEL2HMECIM-PET_C11aR65MCF7CHA-PET_KDEL2MCF7CHA-PET_C11aR65HCC1854IM-PET

.JOG43923.GA:-0.0405219
.JOG43923.GA:-0.0405219

7CHA-PET

$\lambda = 0.0410264$
 $\gamma = 0.0320156, \text{CUAP1-C} = 0.0477839, \text{AL2-C} = 0.048936$
 $\lambda = 0.0293929$
 $\gamma = 0.0418833$

14MCF7-CHA-PET

$\lambda = 0.0297271$

Key (Supplementary Table 5)

Field	Description
browser	hyperlink to UCSC Genome Browser showing 1 Mb around variant
variant	Oncoarray variant ID
chrom	Chromosome
position	Chromosome position, hg19/GRCh37 build
locus	Oncoarray variant ID for top snp at locus
rsID	rsID: multiple IDs may be listed if several rsIDs (dbSNP 138) overlap the same position
rsID_at.same.pos	rsID(s) overlapping this position
TF_motifs/delta	ENCODE_PWM alteration. The delta shown as "+" (PWM strengthened) or "-" (weakened)
TF-ChIP	Transcription factor ChIP-seq from ENCODE and GEO datasets. Format = celltype;target,celltype;target,celltype;target,....
Histone_modifications	Histone modification ChIP-seq. Format = celltype;histonemark,celltype;histonemark,celltype;histonemark,....
ChromHMM_enhancer	Enhancers from 25-state chromatin state segmentation HMM modeling from Roadmap Epigenomics Project. Breast cell types = myoepithelial, HMEC, variant HMEC and MCF7
ChromHMM_promoter	Promoters from 25-state chromatin state segmentation HMM modeling from Roadmap Epigenomics Project. Breast cell types = myoepithelial, HMEC, variant HMEC and MCF7
Open_chromatin	Regions identified by DNase-seq and FAIRE-seq. Data from ENCODE, Roadmap, GEO
RegulomeDB_score	RegulomeDB score. Score (http://regulomedb.org/help#score). Scale: 1 is most likely to be functional, to 7 = least likely.
GWAS_traits	A GWAS signal within 5 kb either direction
Overlapping_RefGene	SNP falls within an annotated RefGene (within transcribed sequence)
RefGeneTSS/distance	Distance to nearest refseq transcription start site
Functional_annotation	RefGene functional annotation
eQTL_target_all	SNP reported to be associated with expression in studies including GTEx.v6, GEUVADIS, Westra Nat Genetics. All tissue types included.
eQTL_GTEx.breast	SNP is associated with expression in GTEx breast samples (N =186)
eQTL_TCGA	Significant eGene from TCGA. Format = Gene1:EffectAllele:Direction:Pvalue1, Gene2:EffectAllele:Direction:Pvalue2... ("+" denotes the effect allele is associated with increased expression)
eQTL_METABRIC	Significant eGene from METABRIC. Format = Gene1:EffectAllele:Direction:Pvalue1, Gene2:EffectAllele:Direction:Pvalue2... ("+" denotes the effect allele is associated with increased expression)
Predicted_target_gene	SNP lies in a putative regulatory element predicted to regulated the listed gene, reported by methods IM-PET, Hnisz, PreSTIGE, Chia-PET, Hi-C, 3C, 4C, 5C, FANTOM5. Format = target:cell:method,.,target:c

Summary of chromatin interaction and enhancer-promoter annotation methods

Method	PMID	Experimental basis	N cell types assayed	Data source	Breast cells	Target annotation
ChIA-PET	22265404	NGS of immunoprecipitated chromatin interactions	5	ENCODE, https://www.encodeproject.org/	MCF7	Intersection of TSS and chromatin interaction
Hi-C	25497547	Genome-wide chromatin interactions	6	NCBI GEO, http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE63525	HMEC	Intersection of TSS and chromatin interaction
Hnisz	24119843	Correlation of H3K27ac levels at enhancers and RNA-seq signals	82	Original publication	MCF7, HMEC, HCC1954	Reported in original publication
PreSTIGE	24196873	Correlation of cell type-specific H3K4me1 levels at enhancers and RNA-seq signals	14	PreSTIGE web resource, http://genetics.case.edu/prestige/	MCF7, HMEC	Reported in original publication
IM-PET	24821768	Correlation of combined H3K4me1, H3K4me3 and H3K27ac levels at enhancers and RNA-seq signals	31	4DGenome web resource, http://4dgenome.int-med.uiowa.edu/	MCF7, HMEC, HCC1954	Reported in original publication and 4DGenome web resource.
FANTOM5	24670763	Correlation of expression at enhancers and promoters by CAGE analysis	113	FANTOM5 web resource, http://enhancer.binf.ku.dk/presets/	Primary breast	TSS reported

ell:method,,,target:cell:method1,method2,,.....

Supplementary Table 6: Data Sources for *in silico* analyses of the 10 novel ER-negative breast cancer susceptibility loci

Filename	Class	Biosample	term	Experiment	target	Biosample	treat	Biological	replic	Accession	BrowserName (cell,target,treatment,note,accession)
GSE41995_AR.bed.gz	tf	MCF-7	AR	none				GFPlagged		GSE41995	MCF-7,AR,none,GFPlagged,GSE41995
GSE74069_AR_ChIP_DHT_4hrs_strigent_tf	tf	MDA-MB-453	AR	DHT	x					GSE74069	MDA-MB-453,AR,DHT,x,GSE74069
GSE74069_AR_ChIP_MPA_4hrs_strigent_tf	tf	MDA-MB-453	AR	MPA	x					GSE74069	MDA-MB-453,AR,MPA,x,GSE74069
GSE74069_AR_ChIP_Veh_4hrs_strigent_tf	tf	MDA-MB-453	AR	Veh	x					GSE74069	MDA-MB-453,AR,Veh,x,GSE74069
GSM1099030_AR-peak.bed.gz	tf	MDA-MB-453	AR	none	x					GSM1099030	MDA-MB-453,AR,none,x,GSM1099030
GSE41995_ATF1.bed.gz	tf	MCF-7	ATF1	none				GFPlagged		GSE41995	MCF-7,ATF1,none,GFPlagged,GSE41995
ENCF001UMJ.bed.gz	tf	MCF-7	CEBPB	none				rep1		ENCF001UMJ	MCF-7,CEBPB,none,rep1,ENCF001UMJ
ENCF001UMK.bed.gz	tf	MCF-7	CEBPB	none				rep2		ENCF001UMK	MCF-7,CEBPB,none,rep2,ENCF001UMK
GSE57498_MCF7_ChromHMM.bed.gz	chromhmm	MCF-7	chromhmm	none	x					GSE57498	MCF-7,chromhmm,none,x,GSE57498
E027_25_imputed12marks_segments.bed.chromhmm	chromhmm	BRST.MYOEP	chromhmm	none	x					RM_E027_25_im	BRST.MYOEP,chromhmm,none,x,RM_E027_25_imputed12marks
E028_25_imputed12marks_segments.bed.chromhmm	chromhmm	BRST.HMEC	chromhmm	none	x					RM_E119_25_im	BRST.HMEC,chromhmm,none,x,RM_E119_25_imputed12marks
E119_25_imputed12marks_segments.bed.chromhmm	chromhmm	BRST.vHMEC	chromhmm	none	x					RM_E028_25_im	BRST.vHMEC,chromhmm,none,x,RM_E028_25_imputed12marks
GSE46166_Peaks_cJun_refl_lgG_200.betf	tf	BT549	cJUN	IgG	x					GSE46166	BT549,cJUN,IgG,x,GSE46166
GSE46166_Peaks_cJun_refl_input_200.betf	tf	BT549	cJUN	input	x					GSE46166	BT549,cJUN,input,x,GSE46166
GSE41995_CREB1.bed.gz	tf	MCF-7	CREB1	none				GFPlagged		GSE41995	MCF-7,CREB1,none,GFPlagged,GSE41995
ENCF001UTR.bed.gz	tf	MCF-7	CTCF	none				rep1		ENCF001UTR	MCF-7,CTCF,none,rep1,ENCF001UTR
ENCF002DBL.bed.gz	tf	MCF-7	CTCF	none	x					ENCF002DBL	MCF-7,CTCF,none,x,ENCF002DBL
ENCF001UML.bed.gz	tf	MCF-7	CTCF	none				rep1		ENCF001UML	MCF-7,CTCF,none,rep1,ENCF001UML
ENCF001UMN.bed.gz	tf	MCF-7	CTCF	none				rep2		ENCF001UMN	MCF-7,CTCF,none,rep2,ENCF001UMN
ENCF001URB.bed.gz	tf	T47D	CTCF	dimethyl_sulfoxid	rep1					ENCF001URB	T47D,CTCF,dimethyl_sulfoxide,rep1,ENCF001URB
ENCF001URC.bed.gz	tf	T47D	CTCF	dimethyl_sulfoxid	rep2					ENCF001URC	T47D,CTCF,dimethyl_sulfoxide,rep2,ENCF001URC
ENCF002CNT.bed.gz	tf	T47D	CTCF	dimethyl_sulfoxid	x					ENCF002CNT	T47D,CTCF,dimethyl_sulfoxide,x,ENCF002CNT
ENCF001SWS.bed.gz	tf	mammary_epithe	CTCF	none	x					ENCF001SWS	mammary_epithelial_cell,CTCF,none,x,ENCF001SWS
ENCF002CEB.bed.gz	tf	mammary_epithe	CTCF	none	x					ENCF002CEB	mammary_epithelial_cell,CTCF,none,x,ENCF002CEB
ENCF001UTQ.bed.gz	tf	MCF-7	CTCF	none				rep1		ENCF001UTQ	MCF-7,CTCF,none,rep1,ENCF001UTQ
ENCF002DBK.bed.gz	tf	MCF-7	CTCF	none	x					ENCF002DBK	MCF-7,CTCF,none,x,ENCF002DBK
ENCF001UTO.bed.gz	tf	MCF-7	CTCF	17b-estradiol	x					ENCF001UTO	MCF-7,CTCF,17b-estradiol,x,ENCF001UTO
ENCF002DBJ.bed.gz	tf	MCF-7	CTCF	17b-estradiol	x					ENCF002DBJ	MCF-7,CTCF,17b-estradiol,x,ENCF002DBJ
ENCF001UTP.bed.gz	tf	MCF-7	CTCF	none	x					ENCF001UTP	MCF-7,CTCF,none,x,ENCF001UTP
ENCF002DBM.bed.gz	tf	MCF-7	CTCF	none	x					ENCF002DBM	MCF-7,CTCF,none,x,ENCF002DBM
ENCF001UTS.bed.gz	tf	MCF-7	CTCF	none	x					ENCF001UTS	MCF-7,CTCF,none,x,ENCF001UTS
ENCF002DBN.bed.gz	tf	MCF-7	CTCF	none	x					ENCF002DBN	MCF-7,CTCF,none,x,ENCF002DBN
ENCF001XSV.bed.gz	tf	MCF-7	CTCF	none				rep1		ENCF001XSV	MCF-7,CTCF,none,rep1,ENCF001XSV
ENCF001XSW.bed.gz	tf	MCF-7	CTCF	none				rep1		ENCF001XSW	MCF-7,CTCF,none,rep1,ENCF001XSW
ENCF001XSX.bed.gz	tf	MCF-7	CTCF	none				rep2		ENCF001XSX	MCF-7,CTCF,none,rep2,ENCF001XSX
ENCF001XSY.bed.gz	tf	MCF-7	CTCF	none				rep2		ENCF001XSY	MCF-7,CTCF,none,rep2,ENCF001XSY
ENCF002DDK.bed.gz	tf	MCF-7	CTCF	none	x					ENCF002DDK	MCF-7,CTCF,none,x,ENCF002DDK
ENCF001XRL.bed.gz	tf	mammary_epithe	CTCF	none				rep1		ENCF001XRL	mammary_epithelial_cell,CTCF,none,rep1,ENCF001XRL
ENCF001XRM.bed.gz	tf	mammary_epithe	CTCF	none				rep2		ENCF001XRM	mammary_epithelial_cell,CTCF,none,rep2,ENCF001XRM
ENCF001XRN.bed.gz	tf	mammary_epithe	CTCF	none				rep1		ENCF001XRN	mammary_epithelial_cell,CTCF,none,rep1,ENCF001XRN
ENCF001XRO.bed.gz	tf	mammary_epithe	CTCF	none				rep2		ENCF001XRO	mammary_epithelial_cell,CTCF,none,rep2,ENCF001XRO
ENCF002DDB.bed.gz	tf	mammary_epithe	CTCF	none	x					ENCF002DDB	mammary_epithelial_cell,CTCF,none,x,ENCF002DDB
GSM1122667_CTCF-SUM159-hg19-sd_q_	tf	SUM159	CTCF	none	x					GSM1122667	SUM159,CTCF,none,x,GSM1122667
ENCF001VPX.bed.gz	tf	MCF_10A	E2F4	afimoxifene	x					ENCF001VPX	MCF_10A,E2F4,afimoxifene,x,ENCF001VPX
ENCF002CZB.bed.gz	tf	MCF_10A	E2F4	afimoxifene	x					ENCF002CZB	MCF_10A,E2F4,afimoxifene,x,ENCF002CZB
GSM1462477_Egln2_peaks.bed.gz	tf	T47D	Egln2	hypoxia	x					GSM1462477	T47D,Egln2,hypoxia,x,GSM1462477
ENCF001UMM.bed.gz	tf	MCF-7	EGR1	none				rep1		ENCF001UMM	MCF-7,EGR1,none,rep1,ENCF001UMM
ENCF001UMO.bed.gz	tf	MCF-7	EGR1	none				rep2		ENCF001UMO	MCF-7,EGR1,none,rep2,ENCF001UMO
ENCF001UMP.bed.gz	tf	MCF-7	ELF1	none				rep1		ENCF001UMP	MCF-7,ELF1,none,rep1,ENCF001UMP
ENCF001UMQ.bed.gz	tf	MCF-7	ELF1	none				rep2		ENCF001UMQ	MCF-7,ELF1,none,rep2,ENCF001UMQ
GSE41995_ELK1.bed.gz	tf	MCF-7	ELK1	none				GFPlagged		GSE41995	MCF-7,ELK1,none,GFPlagged,GSE41995
ENCF001URP.bed.gz	tf	T47D	EP300	dimethyl_sulfoxid	rep1					ENCF001URP	T47D,EP300,dimethyl_sulfoxide,rep1,ENCF001URP
ENCF001URQ.bed.gz	tf	T47D	EP300	dimethyl_sulfoxid	rep2					ENCF001URQ	T47D,EP300,dimethyl_sulfoxide,rep2,ENCF001URQ
ENCF002CNZ.bed.gz	tf	T47D	EP300	dimethyl_sulfoxid	x					ENCF002CNZ	T47D,EP300,dimethyl_sulfoxide,x,ENCF002CNZ
ENCF001UNJ.bed.gz	tf	MCF-7	EP300	none				rep1		ENCF001UNJ	MCF-7,EP300,none,rep1,ENCF001UNJ
ENCF001UNK.bed.gz	tf	MCF-7	EP300	none				rep2		ENCF001UNK	MCF-7,EP300,none,rep2,ENCF001UNK
GSM1187116_s01_MCF7_ER_rep1_macs	tf	MCF-7	ER	E2				rep1		GSM1187116	MCF-7,ER,E2,rep1,GSM1187116
GSM1187117_s02_MCF7_ER_rep2_macs	tf	MCF-7	ER	E2				rep2		GSM1187117	MCF-7,ER,E2,rep2,GSM1187117
GSM1187118_s03_MCF7_ER_rep3_macs	tf	MCF-7	ER	E2				rep3		GSM1187118	MCF-7,ER,E2,rep3,GSM1187118
GSM1669078_jc2334MCF7ERVehRep1.bw	tf	MCF-7	ER	vehicle				rep1		GSM1669078	MCF-7,ER,vehicle,rep1,GSM1669078
GSM1669079_jc2335MCF7ERPER2Rep1.bw	tf	MCF-7	ER	E2				rep1		GSM1669079	MCF-7,ER,E2,rep1,GSM1669079
GSM1669080_jc2336MCF7ERPGRep1.bw	tf	MCF-7	ER	PG				rep1		GSM1669080	MCF-7,ER,PG,rep1,GSM1669080
GSM1669081_jc2337MCF7ERE2+PGRep1.bw	tf	MCF-7	ER	E2+PG				rep1		GSM1669081	MCF-7,ER,E2+PG,rep1,GSM1669081
GSM1669082_jc2338MCF7ERVehRep2.bw	tf	MCF-7	ER	vehicle				rep2		GSM1669082	MCF-7,ER,vehicle,rep2,GSM1669082
GSM1669083_jc2339MCF7ERE2Rep2.bw	tf	MCF-7	ER	E2				rep2		GSM1669083	MCF-7,ER,E2,rep2,GSM1669083
GSM1669084_jc2340MCF7ERPGRep2.bw	tf	MCF-7	ER	PG				rep2		GSM1669084	MCF-7,ER,PG,rep2,GSM1669084
GSM1669085_jc2341MCF7ERE2+PGRep1.bw	tf	MCF-7	ER	E2+PG				rep2		GSM1669085	MCF-7,ER,E2+PG,rep2,GSM1669085
GSM1669086_jc2342MCF7ERVehRep3.bw	tf	MCF-7	ER	vehicle				rep3		GSM1669086	MCF-7,ER,vehicle,rep3,GSM1669086
GSM1669087_jc2343MCF7ERE2Rep3.bw	tf	MCF-7	ER	E2				rep3		GSM1669087	MCF-7,ER,E2,rep3,GSM1669087
GSM1669088_jc2344MCF7ERPGRep3.bw	tf	MCF-7	ER	PG				rep3		GSM1669088	MCF-7,ER,PG,rep3,GSM1669088
GSM1669089_jc2345MCF7ERE2+PGRep1.bw	tf	MCF-7	ER	E2+PG				rep3		GSM1669089	MCF-7,ER,E2+PG,rep3,GSM1669089
GSM1669102_jc2358T47DERVehRep1.bw	tf	T47D	ER	vehicle				rep1		GSM1669102	T47D,ER,vehicle,rep1,GSM1669102
GSM1669103_jc2359T47DERE2Rep1.bw	tf	T47D	ER	E2				rep1		GSM1669103	T47D,ER,E2,rep1,GSM1669103
GSM1669104_jc2360T47DERPGRep1.bw	tf	T47D	ER	PG				rep1		GSM1669104	T47D,ER,PG,rep1,GSM1669104
GSM1669105_jc2361T47DERE2+PGRep1.bw	tf	T47D	ER	E2+PG				rep1		GSM1669105	T47D,ER,E2+PG,rep1,GSM1669105
GSM1669106_jc2362T47DERVehRep2.bw	tf	T47D	ER	vehicle				rep2		GSM1669106	T47D,ER,vehicle,rep2,GSM1669106
GSM1669107_jc2363T47DERE2Rep2.bw	tf	T47D	ER	E2				rep2		GSM1669107	T47D,ER,E2,rep2,GSM1669107
GSM1669108_jc2364T47DERPGRep2.bw	tf	T47D	ER	PG				rep2		GSM1669108	T47D,ER,PG,rep2,GSM1669108
GSM1669109_jc2365T47DERE2+PGRep2.bw	tf	T47D	ER	E2+PG				rep2		GSM1669109	T47D,ER,E2+PG,rep2,GSM1669109
GSM1669110_jc2366T47DERVehRep3.bw	tf	T47D	ER	vehicle				rep3		GSM1669110	T47D,ER,vehicle,rep3,GSM1669110
GSM1669111_jc2367T47DERE2Rep3.bw	tf	T47D	ER	E2				rep3		GSM1669111	T47D,ER,E2,rep3,GSM1669111
GSM1669112_jc2368T47DERPGRep3.bw	tf	T47D	ER	PG				rep3		GSM1669112	T47D,ER,PG,rep3,GSM1669112
GSM1669113_jc2369T47DERE2+PGRep3.bw	tf	T47D	ER	E2+PG				rep3		GSM1669113	T47D,ER,E2+PG,rep3,GSM1669113
GSM986059_JC349_ER_siINT_E2_1_macs	tf	MCF-7	ER	siINT						GSM986059	MCF-7,ER,E2,siINT,GSM986059
GSM986060_JC350_ER_siGATA_E2_1_rtf	tf	MCF-7	ER	siGATA						GSM986060	MCF-7,ER,E2,siGATA,GSM986060
GSM986061_JC406_ER_siINT_E2_2_macs	tf	MCF-7	ER	siINT						GSM986061	MCF-7,ER,E2,siINT,GSM986061
GSM986062_JC407_ER_siGATA_E2_2_rtf	tf	MCF-7	ER	siGATA						GSM986062	MCF-7,ER,E2,siGATA,GSM986062
GSM986063_JC471_ER_siINT_E2_3_macs	tf	MCF-7	ER	siINT						GSM986063	MCF-7,ER,E2,siINT,GSM986063
GSM986064_JC472_ER_siGATA_E2_3_rtf	tf	MCF-7	ER	siGATA						GSM986064	MCF-7,ER,E2,siGATA,GSM986064
GSM986089_JC589_ER_siINT_E2_1_macs	tf	ZR751	ER	siINT						GSM986089	ZR751,ER,E2,siINT,GSM986089
GSM986090_JC590_ER_siGATA_E2_1_rtf	tf	ZR751	ER	siGATA						GSM986090	ZR751,ER,E2,siGATA,GSM986090
GSM1038222_ERalphainERacells.bed.gz	tf	MCF-7	ERalpha	E2				ERa.cells		GSM1038222	MCF-7,ERalpha,E2,ERa.cells,GSM1038222
GSM1038223_ERalphainERabcells.bed.gz	tf	MCF-7	ERalpha	E2				ERab.cells		GSM1038223	MCF-7,ERalpha,E2,ERab.cells,GSM1038223
GSM862178_t0_export.txt_unique.EE_W1	tf	MCF-7	ERalpha	t0	x					GSM862178	MCF-7,ERalpha,t0,x,GSM862178
GSM862179_t1_export.txt_unique.EE_W1	tf	MCF-7	ERalpha	t1	x					GSM862179	MCF-7,ERalpha,t1,x,GSM862179
GSM862180_t4_export.txt_unique.EE_W1	tf	MCF-7	ERalpha	t4	x					GSM862180	MCF-7,ERalpha,t4,x,GSM862180

GSM862181_t24_export.txt_unique.EE_W	tf	MCF-7	ERalpha	t24	x	GSM862181	MCF-7,ERalpha,t24,x,GSM862181
GSM1038224_ERbetainERabcells.bed.gz	tf	MCF-7	ERbeta	E2	ERab.cells	GSM1038224	MCF-7,ERbeta,E2,ERab.cells,GSM1038224
GSM1038225_ERbetainERbCells.bed.gz	tf	MCF-7	ERbeta	E2	ERb.cells	GSM1038225	MCF-7,ERbeta,E2,ERb.cells,GSM1038225
ENCF001URF.bed.gz	tf	T47D	ESR1	genistein	rep1	ENCF001URF	T47D,ESR1,genistein,rep1,ENCF001URF
ENCF001URG.bed.gz	tf	T47D	ESR1	genistein	rep2	ENCF001URG	T47D,ESR1,genistein,rep2,ENCF001URG
ENCF002CNV.bed.gz	tf	T47D	ESR1	genistein	x	ENCF002CNV	T47D,ESR1,genistein,x,ENCF002CNV
ENCF001URD.bed.gz	tf	T47D	ESR1	bisphenol_A	rep1	ENCF001URD	T47D,ESR1,bisphenol_A,rep1,ENCF001URD
ENCF001URE.bed.gz	tf	T47D	ESR1	bisphenol_A	rep2	ENCF001URE	T47D,ESR1,bisphenol_A,rep2,ENCF001URE
ENCF002CNU.bed.gz	tf	T47D	ESR1	bisphenol_A	x	ENCF002CNU	T47D,ESR1,bisphenol_A,x,ENCF002CNU
ENCF001URH.bed.gz	tf	T47D	ESR1	estradiol	rep1	ENCF001URH	T47D,ESR1,estradiol,rep1,ENCF001URH
ENCF001URI.bed.gz	tf	T47D	ESR1	estradiol	rep2	ENCF001URI	T47D,ESR1,estradiol,rep2,ENCF001URI
ENCF002CNW.bed.gz	tf	T47D	ESR1	estradiol	x	ENCF002CNW	T47D,ESR1,estradiol,x,ENCF002CNW
GSE41995_ESR1.bed.gz	tf	MCF-7	ESR1	none	GFPtagged	GSE41995	MCF-7,ESR1,none,GFPtagged,GSE41995
ENCF001VPR.bed.gz	tf	MCF_10A	FOS	ethanol	x	ENCF001VPR	MCF_10A,FOS,ethanol,x,ENCF001VPR
ENCF002CYV.bed.gz	tf	MCF_10A	FOS	ethanol	x	ENCF002CYV	MCF_10A,FOS,ethanol,x,ENCF002CYV
ENCF001VPT.bed.gz	tf	MCF_10A	FOS	afimoxifene	x	ENCF001VPT	MCF_10A,FOS,afimoxifene,x,ENCF001VPT
ENCF001SWW.bed.gz	histone	mammary_epithe	H3K27ac	none	x	ENCF001SWW	mammary_epithelial_cell,H3K27ac,none,x,ENCF001SWW
ENCF001VCU.bed.gz	histone	MCF-7	H3K27ac	none	x	ENCF001VCU	MCF-7,H3K27ac,none,x,ENCF001VCU
GSE49651_MDAMB231.H3K27Ac.hg19.all	histone	MDA-MB-231	H3K27ac	none	x	GSE49651	MDA-MB-231,H3K27ac,none,x,GSE49651
ENCF002CYX.bed.gz	tf	MCF_10A	FOS	afimoxifene	x	ENCF002CYX	MCF_10A,FOS,afimoxifene,x,ENCF002CYX
ENCF001VPU.bed.gz	tf	MCF_10A	FOS	afimoxifene	x	ENCF001VPU	MCF_10A,FOS,afimoxifene,x,ENCF001VPU
ENCF002CYY.bed.gz	tf	MCF_10A	FOS	afimoxifene	x	ENCF002CYY	MCF_10A,FOS,afimoxifene,x,ENCF002CYY
ENCF001VPS.bed.gz	tf	MCF_10A	FOS	afimoxifene	x	ENCF001VPS	MCF_10A,FOS,afimoxifene,x,ENCF001VPS
GSM986077_JC622_H3K27ac_siINT_E2_1	histone	MCF-7	H3K27ac	E2	siINT	GSM986077	MCF-7,H3K27ac,E2,siINT,GSM986077
ENCF002CYW.bed.gz	tf	MCF_10A	FOS	afimoxifene	x	ENCF002CYW	MCF_10A,FOS,afimoxifene,x,ENCF002CYW
GSE41995_FOS.bed.gz	tf	MCF-7	FOS	none	GFPtagged	GSE41995	MCF-7,FOS,none,GFPtagged,GSE41995
GSE41995_FOSB.bed.gz	tf	MCF-7	FOSB	none	GFPtagged	GSE41995	MCF-7,FOSB,none,GFPtagged,GSE41995
GSE41995_FOSL1.bed.gz	tf	MCF-7	FOSL1	none	GFPtagged	GSE41995	MCF-7,FOSL1,none,GFPtagged,GSE41995
ENCF001UMR.bed.gz	tf	MCF-7	FOSL2	none	rep1	ENCF001UMR	MCF-7,FOSL2,none,rep1,ENCF001UMR
GSM986078_JC624_H3K27ac_siGATA_E1	histone	MCF-7	H3K27ac	E2	siGATA	GSM986078	MCF-7,H3K27ac,E2,siGATA,GSM986078
ENCF001UMS.bed.gz	tf	MCF-7	FOSL2	none	rep2	ENCF001UMS	MCF-7,FOSL2,none,rep2,ENCF001UMS
GSE41995_FOSL2.bed.gz	tf	MCF-7	FOSL2	none	GFPtagged	GSE41995	MCF-7,FOSL2,none,GFPtagged,GSE41995
ENCF001URJ.bed.gz	tf	T47D	FOXA1	dimethyl_sulfoxid	rep1	ENCF001URJ	T47D,FOXA1,dimethyl_sulfoxide,rep1,ENCF001URJ
ENCF001URK.bed.gz	tf	T47D	FOXA1	dimethyl_sulfoxid	rep2	ENCF001URK	T47D,FOXA1,dimethyl_sulfoxide,rep2,ENCF001URK
ENCF002CNX.bed.gz	tf	T47D	FOXA1	dimethyl_sulfoxid	x	ENCF002CNX	T47D,FOXA1,dimethyl_sulfoxide,x,ENCF002CNX
GSM986079_JC621_H3K27ac_siINT_Veh_1	histone	MCF-7	H3K27ac	Veh	siNT	GSM986079	MCF-7,H3K27ac,Veh,siNT,GSM986079
GSM986080_JC623_H3K27ac_siGATA_V1	histone	MCF-7	H3K27ac	Veh	siGATA	GSM986080	MCF-7,H3K27ac,Veh,siGATA,GSM986080
GSE41995_FOXA1.bed.gz	tf	MCF-7	FOXA1	none	GFPtagged	GSE41995	MCF-7,FOXA1,none,GFPtagged,GSE41995
GSM1099031_FOXA1-peak.bed.gz	tf	MDA-MB-453	FOXA1	none	x	GSM1099031	MDA-MB-453,FOXA1,none,x,GSM1099031
GSM986065_JC731_FoxA1_siINT_Veh_N4	tf	MCF-7	FoxA1	Veh	siNT	GSM986065	MCF-7,FoxA1,Veh,siNT,GSM986065
GSM986066_JC732_FoxA1_siGATA_Veh_1	tf	MCF-7	FoxA1	Veh	siGATA	GSM986066	MCF-7,FoxA1,Veh,siGATA,GSM986066
E119-H3K27ac.narrowPeak.gz	histone	BRST.vHMEC	H3K27ac	none	x	RM_E119-H3K27ac	BRST.vHMEC,H3K27ac,none,x,RM_E119-H3K27ac
ENCF001UMT.bed.gz	tf	MCF-7	FOXM1	none	rep1	ENCF001UMT	MCF-7,FOXM1,none,rep1,ENCF001UMT
ENCF001UMU.bed.gz	tf	MCF-7	FOXM1	none	rep2	ENCF001UMU	MCF-7,FOXM1,none,rep2,ENCF001UMU
GSM1000995_ds001_mcf7_dmsol.macs_p1	tf	MCF-7	FOXM1	dmsol	x	GSM1000995	MCF-7,FOXM1,dmsol,x,GSM1000995
GSM1000996_ds002_mcf7_ts.macs_peak1	tf	MCF-7	FOXM1	ts	x	GSM1000996	MCF-7,FOXM1,ts,x,GSM1000996
GSM1000997_ds003_mcf7_dmsol.macs_p1	tf	MCF-7	FOXM1	dmsol	x	GSM1000997	MCF-7,FOXM1,dmsol,x,GSM1000997
GSM1000998_ds004_mcf7_ts.macs_peak1	tf	MCF-7	FOXM1	ts	x	GSM1000998	MCF-7,FOXM1,ts,x,GSM1000998
GSM1000999_ds005_mdaz31_dmsol.macs_t1	tf	MDA-MB-231	FOXM1	dmsol	x	GSM1000999	MDA-MB-231,FOXM1,dmsol,x,GSM1000999
GSM1001000_ds006_mdaz31_ts.macs_p1	tf	MDA-MB-231	FOXM1	ts	x	GSM1001000	MDA-MB-231,FOXM1,ts,x,GSM1001000
GSM1001001_ds007_mdaz31_dmsol.macs_t1	tf	MDA-MB-231	FOXM1	dmsol	x	GSM1001001	MDA-MB-231,FOXM1,dmsol,x,GSM1001001
GSM1001002_ds008_mdaz31_ts.macs_p1	tf	MDA-MB-231	FOXM1	ts	x	GSM1001002	MDA-MB-231,FOXM1,ts,x,GSM1001002
GSM1001003_ds011_mcf7_dmsol.macs_p1	tf	MCF-7	FOXM1	dmsol	x	GSM1001003	MCF-7,FOXM1,dmsol,x,GSM1001003
GSM1001004_ds012_mcf7_ts.macs_peak1	tf	MCF-7	FOXM1	ts	x	GSM1001004	MCF-7,FOXM1,ts,x,GSM1001004
GSM1001005_ds017_mcf7_dmsol.macs_p1	tf	MCF-7	FOXM1	dmsol	x	GSM1001005	MCF-7,FOXM1,dmsol,x,GSM1001005
GSM1001006_ds018_mcf7_ts.macs_peak1	tf	MCF-7	FOXM1	ts	x	GSM1001006	MCF-7,FOXM1,ts,x,GSM1001006
GSE46166_Peaks_fra1_refl_lg200.bed.t1	tf	BT549	FRA1	IgG	x	GSE46166	BT549,FRA1,IgG,x,GSE46166
GSE46166_Peaks_fra1_refl_input_200.bert1	tf	BT549	FRA1	input	x	GSE46166	BT549,FRA1,input,x,GSE46166
ENCF001UMV.bed.gz	tf	MCF-7	GABPA	none	rep1	ENCF001UMV	MCF-7,GABPA,none,rep1,ENCF001UMV
ENCF001UMW.bed.gz	tf	MCF-7	GABPA	none	rep2	ENCF001UMW	MCF-7,GABPA,none,rep2,ENCF001UMW
ENCF001VQG.bed.gz	tf	MCF-7	GATA3	none	x	ENCF001VQG	MCF-7,GATA3,none,x,ENCF001VQG
ENCF002CZK.bed.gz	tf	MCF-7	GATA3	none	x	ENCF002CZK	MCF-7,GATA3,none,x,ENCF002CZK
ENCF001URL.bed.gz	tf	T47D	GATA3	dimethyl_sulfoxid	rep1	ENCF001URL	T47D,GATA3,dimethyl_sulfoxide,rep1,ENCF001URL
ENCF001URM.bed.gz	tf	T47D	GATA3	dimethyl_sulfoxid	rep2	ENCF001URM	T47D,GATA3,dimethyl_sulfoxide,rep2,ENCF001URM
ENCF002CNY.bed.gz	tf	T47D	GATA3	dimethyl_sulfoxid	x	ENCF002CNY	T47D,GATA3,dimethyl_sulfoxide,x,ENCF002CNY
ENCF001UMX.bed.gz	tf	MCF-7	GATA3	none	rep1	ENCF001UMX	MCF-7,GATA3,none,rep1,ENCF001UMX
ENCF001UMZ.bed.gz	tf	MCF-7	GATA3	none	rep2	ENCF001UMZ	MCF-7,GATA3,none,rep2,ENCF001UMZ
ENCF001VOF.bed.gz	tf	MCF-7	GATA3	none	x	ENCF001VOF	MCF-7,GATA3,none,x,ENCF001VOF
ENCF002CZJ.bed.gz	tf	MCF-7	GATA3	none	x	ENCF002CZJ	MCF-7,GATA3,none,x,ENCF002CZJ
GSE41995_GATA3.bed.gz	tf	MCF-7	GATA3	none	GFPtagged	GSE41995	MCF-7,GATA3,none,GFPtagged,GSE41995
GSM986067_JC315_GATA3_E2_1_macs_t1	tf	MCF-7	GATA3	E2	x	GSM986067	MCF-7,GATA3,E2,x,GSM986067
GSM986068_JC314_GATA3_Veh_1_macs_t1	tf	MCF-7	GATA3	Veh	x	GSM986068	MCF-7,GATA3,Veh,x,GSM986068
GSM986069_JC427_GATA3_E2_2_macs_t1	tf	MCF-7	GATA3	E2	x	GSM986069	MCF-7,GATA3,E2,x,GSM986069
GSM986070_JC426_GATA3_Veh_2_macs_t1	tf	MCF-7	GATA3	Veh	x	GSM986070	MCF-7,GATA3,Veh,x,GSM986070
GSM986071_JC485_GATA3_E2_3_macs_t1	tf	MCF-7	GATA3	E2	x	GSM986071	MCF-7,GATA3,E2,x,GSM986071
GSM986072_JC484_GATA3_Veh_3_macs_t1	tf	MCF-7	GATA3	Veh	x	GSM986072	MCF-7,GATA3,Veh,x,GSM986072
GSM986073_JC556_GATA3_E2_4_macs_t1	tf	MCF-7	GATA3	E2	x	GSM986073	MCF-7,GATA3,E2,x,GSM986073
GSM986074_JC555_GATA3_Veh_4_macs_t1	tf	MCF-7	GATA3	Veh	x	GSM986074	MCF-7,GATA3,Veh,x,GSM986074
GSM986075_JC633_GATA3_E2_5_macs_t1	tf	MCF-7	GATA3	E2	x	GSM986075	MCF-7,GATA3,E2,x,GSM986075
GSM986076_JC632_GATA3_Veh_5_macs_t1	tf	MCF-7	GATA3	Veh	x	GSM986076	MCF-7,GATA3,Veh,x,GSM986076
ENCF001SWZ.bed.gz	histone	mammary_epithe	H3K4me1	none	x	ENCF001SWZ	mammary_epithelial_cell,H3K4me1,none,x,ENCF001SWZ
GSE49651_MDAMB231.H3K4me1.hg19.all	histone	MDA-MB-231	H3K4me1	none	x	GSE49651	MDA-MB-231,H3K4me1,none,x,GSE49651
GSM986081_JC618_H3K4me1_siNT_E2_1	histone	MCF-7	H3K4me1	E2	siNT	GSM986081	MCF-7,H3K4me1,E2,siNT,GSM986081
GSM986082_JC620_H3K4me1_siGATA_E1	histone	MCF-7	H3K4me1	E2	siGATA	GSM986082	MCF-7,H3K4me1,E2,siGATA,GSM986082
GSM986083_JC617_H3K4me1_siNT_Veh_1	histone	MCF-7	H3K4me1	Veh	siNT	GSM986083	MCF-7,H3K4me1,Veh,siNT,GSM986083
GSM986084_JC619_H3K4me1_siGATA_V1	histone	MCF-7	H3K4me1	Veh	siGATA	GSM986084	MCF-7,H3K4me1,Veh,siGATA,GSM986084
GSE42617_H3K4ME1.bed.gz	histone	MCF-7	H3K4me1	none	x	GSE42617	MCF-7,H3K4me1,none,x,GSE42617
E027-H3K4me1.narrowPeak.gz	histone	BRST.MYOEP	H3K4me1	none	x	RM_E027-H3K4n	BRST.MYOEP,H3K4me1,none,x,RM_E027-H3K4me1
E028-H3K4me1.narrowPeak.gz	histone	BRST.HMEC	H3K4me1	none	x	RM_E028-H3K4n	BRST.HMEC,H3K4me1,none,x,RM_E028-H3K4me1
E119-H3K4me1.narrowPeak.gz	histone	BRST.vHMEC	H3K4me1	none	x	RM_E119-H3K4n	BRST.vHMEC,H3K4me1,none,x,RM_E119-H3K4me1
ENCF001SXA.bed.gz	histone	mammary_epithe	H3K4me2	none	x	ENCF001SXA	mammary_epithelial_cell,H3K4me2,none,x,ENCF001SXA
ENCF476WFI.bed.gz	histone	MCF-7	H3K4me2	none	rep1	ENCF476WFI	MCF-7,H3K4me2,none,rep1,ENCF476WFI
ENCF696NQQ.bed.gz	histone	MCF-7	H3K4me2	none	rep2	ENCF696NQQ	MCF-7,H3K4me2,none,rep2,ENCF696NQQ
ENCF258OSE.bed.gz	histone	MCF-7	H3K4me2	none	rep_1-2-2016	ENCF258OSE	MCF-7,H3K4me2,none,rep_1-2-2016,ENCF258OSE
ENCF457GJC.bed.gz	histone	MCF-7	H3K4me2	none	rep_1-2-2016	ENCF457GJC	MCF-7,H3K4me2,none,rep_1-2-2016,ENCF457GJC
GSM1122654_H3K4me2-MCF7-hg19-sd-q	histone	MCF-7	H3K4me2	none	x	GSM1122654	MCF-7,H3K4me2,none,x,GSM1122654
GSM1122655_H3K4me2-siJarid1b-MCF7	histone	MCF-7	H3K4me2	siJarid1b	x	GSM1122655	MCF-7,H3K4me2,siJarid1b,x,GSM1122655
GSM1122665_H3K4me2-SUM159-hg19-sc	histone	SUM159	H3K4me2	none	x	GSM1122665	SUM159,H3K4me2,none,x,GSM1122665
GSM1402462_H3K4me2-HCC2157-hg19	histone	HCC2157	H3K4me2	none	x	GSM1402462	HCC2157,H3K4me2,none,x,GSM1402462
GSM916108_H3K4me2_LTED_Hg19_Lupi	histone	MCF-7-LTED	H3K4me2	none	x	GSM916108	MCF-7-LTED,H3K4me2,none,x,GSM916108
E119-H3K4me2.narrowPeak.gz	histone	BRST.vHMEC	H3K4me2	none	x	RM_E119-H3K4n	BRST.vHMEC,H3K4me2,none,x,RM_E119-H3K4me2

GSM2037450_HAUSP_MDA_MB_231_CHtf	MDA-MB-231	HAUSP	none	x	GSM2037450	MDA-MB-231_HAUSP,none,x,GSM2037450
ENCF001UMY.bed.gz	MCF-7	HDAC2	none	rep1	ENCF001UMY	MCF-7,HDAC2,none,rep1,ENCF001UMY
ENCF001UNA.bed.gz	MCF-7	HDAC2	none	rep2	ENCF001UNA	MCF-7,HDAC2,none,rep2,ENCF001UNA
GSM1462475_H1F1alpha_peaks.bed.gz	T47D	H1F1alpha	hypoxia	x	GSM1462475	T47D,H1F1alpha,hypoxia,x,GSM1462475
GSM1462476_H1F1beta_peaks.bed.gz	T47D	H1F1beta	hypoxia	x	GSM1462476	T47D,H1F1beta,hypoxia,x,GSM1462476
GSE47164_AF1_HOXB7_MACS_peaks.bed.gz	BT474	HOXB7	none	rep1	GSE47164	BT474,HOXB7,none,rep1,GSE47164
GSE47164_AF2_HOXB7_MACS_peaks.bed.gz	BT474	HOXB7	none	rep1	GSE47164	BT474,HOXB7,none,rep1,GSE47164
GSM1122651_JARID1B-MCF7-hg19-sd-q.tf	MCF-7	JARID1B	none	x	GSM1122651	MCF-7,JARID1B,none,x,GSM1122651
GSM1122652_JARID1B-MCF7-siJARID1B.tf	MCF-7	JARID1B	siJARID1B	x	GSM1122652	MCF-7,JARID1B,siJARID1B,x,GSM1122652
GSM1122653_JARID1B-MCF7-siCTCF-hg19.tf	MCF-7	JARID1B	siCTCF	x	GSM1122653	MCF-7,JARID1B,siCTCF,x,GSM1122653
GSM1122659_JARID1B-T47D-hg19-sd-q.tf	T47D	JARID1B	none	x	GSM1122659	T47D,JARID1B,none,x,GSM1122659
GSM1122661_JARID1B-SUM185-hg19-sd.tf	SUM185	JARID1B	none	x	GSM1122661	SUM185,JARID1B,none,x,GSM1122661
GSM1122662_JARID1B-SUM185-siCTCF.tf	SUM185	JARID1B	siCTCF	x	GSM1122662	SUM185,JARID1B,siCTCF,x,GSM1122662
GSM1122664_JARID1B-SUM159-hg19-sd.tf	SUM159	JARID1B	none	x	GSM1122664	SUM159,JARID1B,none,x,GSM1122664
GSM1122669_JARID1B-MDA231-hg19-sd.tf	MDA231	JARID1B	none	x	GSM1122669	MDA231,JARID1B,none,x,GSM1122669
GSM1122671_JARID1B-HCC2157-hg19-si.tf	HCC2157	JARID1B	none	x	GSM1122671	HCC2157,JARID1B,none,x,GSM1122671
GSE41995_JUN.bed.gz	MCF-7	JUN	none	GFPTagged	GSE41995	MCF-7,JUN,none,GFPTagged,GSE41995
GSE66081_MDA-MB-231_JUN_IDR_0.01.tf	MDA-MB-231	JUN	none	x	GSE66081	MDA-MB-231,JUN,none,x,GSE66081
GSM1848883_36noTNFJun_35lgG_peaks.tf	BT549	JUN	noTNF	IgG	GSM1848883	BT549,JUN,noTNF,IgG,GSM1848883
GSM1848883_noTNFJun36_Input38_peak.tf	BT549	JUN	noTNF	input	GSM1848883	BT549,JUN,noTNF,input,GSM1848883
GSM1848885_39TNFJun_35lgG_peaks.bed.gz	BT549	JUN	TNF	IgG	GSM1848885	BT549,JUN,TNF,IgG,GSM1848885
GSM1848885_TNFJun39_Input38_peaks.tf	BT549	JUN	TNF	input	GSM1848885	BT549,JUN,TNF,input,GSM1848885
GSE41995_JUNB.bed.gz	MCF-7	JUNB	none	GFPTagged	GSE41995	MCF-7,JUNB,none,GFPTagged,GSE41995
ENCF001UNB.bed.gz	MCF-7	JUND	none	rep1	ENCF001UNB	MCF-7,JUND,none,rep1,ENCF001UNB
ENCF001UNC.bed.gz	MCF-7	JUND	none	rep2	ENCF001UNC	MCF-7,JUND,none,rep2,ENCF001UNC
ENCF001URN.bed.gz	T47D	JUND	none	rep1	ENCF001URN	T47D,JUND,none,rep1,ENCF001URN
ENCF001URO.bed.gz	T47D	JUND	none	rep2	ENCF001URO	T47D,JUND,none,rep2,ENCF001URO
GSE41995_JUND.bed.gz	MCF-7	JUND	none	GFPTagged	GSE41995	MCF-7,JUND,none,GFPTagged,GSE41995
ENCF001UND.bed.gz	MCF-7	MAX	none	rep1	ENCF001UND	MCF-7,MAX,none,rep1,ENCF001UND
ENCF001UNE.bed.gz	MCF-7	MAX	none	rep2	ENCF001UNE	MCF-7,MAX,none,rep2,ENCF001UNE
ENCF001UTL.bed.gz	MCF-7	MYC	none	rep1	ENCF001UTL	MCF-7,MYC,none,rep1,ENCF001UTL
ENCF002DBG.bed.gz	MCF-7	MYC	none	x	ENCF002DBG	MCF-7,MYC,none,x,ENCF002DBG
ENCF001UTN.bed.gz	MCF-7	MYC	none	x	ENCF001UTN	MCF-7,MYC,none,x,ENCF001UTN
ENCF002DBI.bed.gz	MCF-7	MYC	none	x	ENCF002DBI	MCF-7,MYC,none,x,ENCF002DBI
ENCF001VPW.bed.gz	MCF_10A	MYC	afimoxifene	x	ENCF001VPW	MCF_10A,MYC,afimoxifene,x,ENCF001VPW
ENCF002CZA.bed.gz	MCF_10A	MYC	afimoxifene	x	ENCF002CZA	MCF_10A,MYC,afimoxifene,x,ENCF002CZA
ENCF001UTM.bed.gz	MCF-7	MYC	none	rep1	ENCF001UTM	MCF-7,MYC,none,rep1,ENCF001UTM
ENCF002DBH.bed.gz	MCF-7	MYC	none	x	ENCF002DBH	MCF-7,MYC,none,x,ENCF002DBH
ENCF001UTK.bed.gz	MCF-7	MYC	17b-estradiol	rep1	ENCF001UTK	MCF-7,MYC,17b-estradiol,rep1,ENCF001UTK
ENCF002DBF.bed.gz	MCF-7	MYC	17b-estradiol	x	ENCF002DBF	MCF-7,MYC,17b-estradiol,x,ENCF002DBF
ENCF001VPV.bed.gz	MCF_10A	MYC	ethanol	x	ENCF001VPV	MCF_10A,MYC,ethanol,x,ENCF001VPV
ENCF002CYZ.bed.gz	MCF_10A	MYC	ethanol	x	ENCF002CYZ	MCF_10A,MYC,ethanol,x,ENCF002CYZ
GSM1099029_MYC-peak.bed.gz	MDA-MB-453	MYC	none	x	GSM1099029	MDA-MB-453,MYC,none,x,GSM1099029
GSE41995_NR1D1.bed.gz	MCF-7	NR1D1	none	GFPTagged	GSE41995	MCF-7,NR1D1,none,GFPTagged,GSE41995
GSE41995_NR1D2.bed.gz	MCF-7	NR1D2	none	GFPTagged	GSE41995	MCF-7,NR1D2,none,GFPTagged,GSE41995
GSE41995_NR1H3.bed.gz	MCF-7	NR1H3	none	GFPTagged	GSE41995	MCF-7,NR1H3,none,GFPTagged,GSE41995
GSE41995_NR2C1-L.bed.gz	MCF-7	NR2C1-L	none	GFPTagged	GSE41995	MCF-7,NR2C1-L,none,GFPTagged,GSE41995
GSE41995_NR2C1-S.bed.gz	MCF-7	NR2C1-S	none	GFPTagged	GSE41995	MCF-7,NR2C1-S,none,GFPTagged,GSE41995
GSE41995_NR2C2.bed.gz	MCF-7	NR2C2	none	GFPTagged	GSE41995	MCF-7,NR2C2,none,GFPTagged,GSE41995
GSE41995_NR2F1.bed.gz	MCF-7	NR2F1	none	GFPTagged	GSE41995	MCF-7,NR2F1,none,GFPTagged,GSE41995
ENCF001UNF.bed.gz	MCF-7	NR2F2	none	rep1	ENCF001UNF	MCF-7,NR2F2,none,rep1,ENCF001UNF
ENCF001UNG.bed.gz	MCF-7	NR2F2	none	rep2	ENCF001UNG	MCF-7,NR2F2,none,rep2,ENCF001UNG
GSE41995_NR2F2.bed.gz	MCF-7	NR2F2	none	GFPTagged	GSE41995	MCF-7,NR2F2,none,GFPTagged,GSE41995
GSE41995_NR3C1.bed.gz	MCF-7	NR3C1	none	GFPTagged	GSE41995	MCF-7,NR3C1,none,GFPTagged,GSE41995
GSE41995_NR4A1.bed.gz	MCF-7	NR4A1	none	GFPTagged	GSE41995	MCF-7,NR4A1,none,GFPTagged,GSE41995
GSE41995_NR4A2.bed.gz	MCF-7	NR4A2	none	GFPTagged	GSE41995	MCF-7,NR4A2,none,GFPTagged,GSE41995
GSM1462478_NRF1_peaks.bed.gz	T47D	NRF1	hypoxia	x	GSM1462478	T47D,NRF1,hypoxia,x,GSM1462478
wgEncodeAwgDnaseDukeMcf7hypoxiaUni dnase	MCF-7	open-chrom	hypoxia	x	ENC_dnase	MCF-7,open-chrom,hypoxia,x,ENC_dnase
wgEncodeAwgDnaseDukeT47DUniPk.narr dnase	T47D	open-chrom	none	x	ENC_dnase	T47D,open-chrom,none,x,ENC_dnase
wgEncodeAwgDnaseUwdukeHmecUniPk.r dnase	HMEC	open-chrom	none	x	ENC_dnase	HMEC,open-chrom,none,x,ENC_dnase
wgEncodeAwgDnaseUwdukeMcf7UniPk.n dnase	MCF-7	open-chrom	none	x	ENC_dnase	MCF-7,open-chrom,none,x,ENC_dnase
GSE42617_FAIRE.bed.gz	MCF-7	open-chrom	none	x	GSE42617	MCF-7,open-chrom,none,x,GSE42617
GSM1122847_HMEC_FAIRE_1.peaksMos faire	HMEC	open-chrom	none	x	GSM1122847	HMEC,open-chrom,none,x,GSM1122847
GSM1122848_HMEC_FAIRE_2.peaksMos faire	HMEC	open-chrom	none	x	GSM1122848	HMEC,open-chrom,none,x,GSM1122848
GSM925735_FAIRE_H19_LTED_rep1.bed faire	MCF-7-LTED	open-chrom	none	rep1	GSM925735	MCF-7-LTED,open-chrom,none,rep1,GSM925735
GSM925736_FAIRE_H19_LTED_rep2.bed faire	MCF-7-LTED	open-chrom	none	rep2	GSM925736	MCF-7-LTED,open-chrom,none,rep2,GSM925736
E028-DNase.hotspot.all.peaks.bed.gz dnase	BRST.HMEC	open-chrom	none	all	RM_E028-DNase	BRST.HMEC,open-chrom,none,all,RM_E028-DNase
E028-DNase.hotspot.fdr0.01.peaks.bed.gz dnase	BRST.HMEC	open-chrom	none	fdr0.01	RM_E028-DNase	BRST.HMEC,open-chrom,none,fdr0.01,RM_E028-DNase
E028-DNase.macs2.narrowPeak.gz dnase	BRST.HMEC	open-chrom	none	x	RM_E028-DNase	BRST.HMEC,open-chrom,none,x,RM_E028-DNase
E119-DNase.macs2.narrowPeak.gz dnase	BRST.vHMEC	open-chrom	none	x	RM_E119-DNase	BRST.vHMEC,open-chrom,none,x,RM_E119-DNase
GSM986085_JC476_p300_siNT_E2_2.mcf	MCF-7	p300	E2	siNT	GSM986085	MCF-7,p300,E2,siNT,GSM986085
GSM986086_JC478_p300_siGATA_E2_2.tf	MCF-7	p300	E2	siGATA	GSM986086	MCF-7,p300,E2,siGATA,GSM986086
GSM986087_JC476_p300_siNT_Veh_2.rtf	MCF-7	p300	Veh	siNT	GSM986087	MCF-7,p300,Veh,siNT,GSM986087
GSM986088_JC477_p300_siGATA_Veh_2.tf	MCF-7	p300	Veh	siGATA	GSM986088	MCF-7,p300,Veh,siGATA,GSM986088
GSM692743_PBX1_MCF7_red_m16_10_5.tf	MCF-7	PBX1	none	x	GSM692743	MCF-7,PBX1,none,x,GSM692743
GSM989353_PBX1_H19_LTED_rep4_wins.tf	MCF-7-LTED	PBX1	none	x	GSM989353	MCF-7-LTED,PBX1,none,x,GSM989353
GSE41995_PGR.bed.gz	MCF-7	PGR	none	GFPTagged	GSE41995	MCF-7,PGR,none,GFPTagged,GSE41995
ENCF001UNL.bed.gz	MCF-7	PML	none	rep1	ENCF001UNL	MCF-7,PML,none,rep1,ENCF001UNL
ENCF001UNM.bed.gz	MCF-7	PML	none	rep2	ENCF001UNM	MCF-7,PML,none,rep2,ENCF001UNM
ENCF001VPZ.bed.gz	MCF_10A	POLR2A	afimoxifene	x	ENCF001VPZ	MCF_10A,POLR2A,afimoxifene,x,ENCF001VPZ
ENCF002CZD.bed.gz	MCF_10A	POLR2A	afimoxifene	x	ENCF002CZD	MCF_10A,POLR2A,afimoxifene,x,ENCF002CZD
ENCF001UTT.bed.gz	MCF-7	POLR2A	none	x	ENCF001UTT	MCF-7,POLR2A,none,x,ENCF001UTT
ENCF002DBQ.bed.gz	MCF-7	POLR2A	none	x	ENCF002DBQ	MCF-7,POLR2A,none,x,ENCF002DBQ
ENCF001UTU.bed.gz	MCF-7	POLR2A	none	rep1	ENCF001UTU	MCF-7,POLR2A,none,rep1,ENCF001UTU
ENCF002DBO.bed.gz	MCF-7	POLR2A	none	x	ENCF002DBO	MCF-7,POLR2A,none,x,ENCF002DBO
ENCF001VPY.bed.gz	MCF_10A	POLR2A	ethanol	x	ENCF001VPY	MCF_10A,POLR2A,ethanol,x,ENCF001VPY
ENCF002CZC.bed.gz	MCF_10A	POLR2A	ethanol	x	ENCF002CZC	MCF_10A,POLR2A,ethanol,x,ENCF002CZC
ENCF001UTV.bed.gz	MCF-7	POLR2A	none	rep1	ENCF001UTV	MCF-7,POLR2A,none,rep1,ENCF001UTV
ENCF002DBP.bed.gz	MCF-7	POLR2A	none	x	ENCF002DBP	MCF-7,POLR2A,none,x,ENCF002DBP
GSE41995_PPARG.bed.gz	MCF-7	PPARG	none	GFPTagged	GSE41995	MCF-7,PPARG,none,GFPTagged,GSE41995
GSE41995_PPARG.bed.gz	MCF-7	PPARG	none	GFPTagged	GSE41995	MCF-7,PPARG,none,GFPTagged,GSE41995
GSM1669090_jc2346MCF7PRVehRep1.bvtf	MCF-7	PR	vehicle	rep1	GSM1669090	MCF-7,PR,vehicle,rep1,GSM1669090
GSM1669091_jc2347MCF7PRE2Rep1.bwtf	MCF-7	PR	E2	rep1	GSM1669091	MCF-7,PR,E2,rep1,GSM1669091
GSM1669092_jc2348MCF7PRPGRep1.bwtf	MCF-7	PR	PG	rep1	GSM1669092	MCF-7,PR,PG,rep1,GSM1669092
GSM1669093_jc2349MCF7PRE2+PGRep.tf	MCF-7	PR	E2+PG	rep1	GSM1669093	MCF-7,PR,E2+PG,rep1,GSM1669093
GSM1669094_jc2350MCF7PRVehRep2.bvtf	MCF-7	PR	vehicle	rep2	GSM1669094	MCF-7,PR,vehicle,rep2,GSM1669094
GSM1669095_jc2351MCF7PRE2Rep2.bwtf	MCF-7	PR	E2	rep2	GSM1669095	MCF-7,PR,E2,rep2,GSM1669095
GSM1669096_jc2352MCF7PRPGRep2.bwtf	MCF-7	PR	PG	rep2	GSM1669096	MCF-7,PR,PG,rep2,GSM1669096
GSM1669097_jc2353MCF7PRE2+PGRep.tf	MCF-7	PR	E2+PG	rep2	GSM1669097	MCF-7,PR,E2+PG,rep2,GSM1669097
GSM1669098_jc2354MCF7PRVehRep3.bvtf	MCF-7	PR	vehicle	rep3	GSM1669098	MCF-7,PR,vehicle,rep3,GSM1669098

GSM1669099_jc2355MCF7PRE2Rep3.bw.tf	MCF-7	PR	E2	rep3	GSM1669099	MCF-7,PR,E2,rep3,GSM1669099
GSM1669100_jc2356MCF7PRPGRep3.bw.tf	MCF-7	PR	PG	rep3	GSM1669100	MCF-7,PR,PG,rep3,GSM1669100
GSM1669101_jc2357MCF7PRE2+PGRep1.bw.tf	MCF-7	PR	E2+PG	rep3	GSM1669101	MCF-7,PR,E2+PG,rep3,GSM1669101
GSM1669114_jc2370T47DPRVehRep1.bw.tf	T47D	PR	vehicle	rep1	GSM1669114	T47D,PR,vehicle,rep1,GSM1669114
GSM1669115_jc2371T47DPRE2Rep1.bw.tf	T47D	PR	E2	rep1	GSM1669115	T47D,PR,E2,rep1,GSM1669115
GSM1669116_jc2372T47DPRPGRep1.bw.tf	T47D	PR	PG	rep1	GSM1669116	T47D,PR,PG,rep1,GSM1669116
GSM1669117_jc2373T47DPRE2+PGRep1.bw.tf	T47D	PR	E2+PG	rep1	GSM1669117	T47D,PR,E2+PG,rep1,GSM1669117
GSM1669118_jc2374T47DPRVehRep2.bw.tf	T47D	PR	vehicle	rep2	GSM1669118	T47D,PR,vehicle,rep2,GSM1669118
GSM1669119_jc2375T47DPRE2Rep2.bw.tf	T47D	PR	E2	rep2	GSM1669119	T47D,PR,E2,rep2,GSM1669119
GSM1669120_jc2376T47DPRPGRep2.bw.tf	T47D	PR	PG	rep2	GSM1669120	T47D,PR,PG,rep2,GSM1669120
GSM1669121_jc2377T47DPRE2+PGRep2.bw.tf	T47D	PR	E2+PG	rep2	GSM1669121	T47D,PR,E2+PG,rep2,GSM1669121
GSM1669122_jc2378T47DPRVehRep3.bw.tf	T47D	PR	vehicle	rep3	GSM1669122	T47D,PR,vehicle,rep3,GSM1669122
GSM1669123_jc2379T47DPRE2Rep3.bw.tf	T47D	PR	E2	rep3	GSM1669123	T47D,PR,E2,rep3,GSM1669123
GSM1669124_jc2380T47DPRPGRep3.bw.tf	T47D	PR	PG	rep3	GSM1669124	T47D,PR,PG,rep3,GSM1669124
GSM1669125_jc2381T47DPRE2+PGRep3.bw.tf	T47D	PR	E2+PG	rep3	GSM1669125	T47D,PR,E2+PG,rep3,GSM1669125
ENCF001UNN.bed.gz	tf	MCF-7	RAD21	none	ENCF001UNN	MCF-7,RAD21,none,rep1,ENCF001UNN
ENCF001UNO.bed.gz	tf	MCF-7	RAD21	none	ENCF001UNO	MCF-7,RAD21,none,rep2,ENCF001UNO
GSE41995_RARA.bed.gz	tf	MCF-7	RARA	none	GSE41995	MCF-7,RARA,none,GFPtagged,GSE41995
GSE41995_RARG.bed.gz	tf	MCF-7	RARG	none	GSE41995	MCF-7,RARG,none,GFPtagged,GSE41995
ENCF001UNH.bed.gz	tf	MCF-7	REST	none	ENCF001UNH	MCF-7,REST,none,rep1,ENCF001UNH
ENCF001UNI.bed.gz	tf	MCF-7	REST	none	ENCF001UNI	MCF-7,REST,none,rep2,ENCF001UNI
GSM1038229_RIP140inERacells.bed.gz	tf	MCF-7	RIP140	E2	GSM1038229	MCF-7,RIP140,E2,ERa.cells,GSM1038229
GSM1038230_RIP140inERabcells.bed.gz	tf	MCF-7	RIP140	E2	GSM1038230	MCF-7,RIP140,E2,ERab.cells,GSM1038230
GSM1038231_RIP140inERbcells.bed.gz	tf	MCF-7	RIP140	E2	GSM1038231	MCF-7,RIP140,E2,ERb.cells,GSM1038231
GSE41995_RORA.bed.gz	tf	MCF-7	RORA	none	GSE41995	MCF-7,RORA,none,GFPtagged,GSE41995
GSE41995_RORC.bed.gz	tf	MCF-7	RORC	none	GSE41995	MCF-7,RORC,none,GFPtagged,GSE41995
GSE41995_RXRA.bed.gz	tf	MCF-7	RXRA	none	GSE41995	MCF-7,RXRA,none,GFPtagged,GSE41995
GSE41995_RXRB.bed.gz	tf	MCF-7	RXRB	none	GSE41995	MCF-7,RXRB,none,GFPtagged,GSE41995
ENCF001UNP.bed.gz	tf	MCF-7	SIN3A	none	ENCF001UNP	MCF-7,SIN3A,none,rep1,ENCF001UNP
ENCF001UNQ.bed.gz	tf	MCF-7	SIN3A	none	ENCF001UNQ	MCF-7,SIN3A,none,rep2,ENCF001UNQ
GSE41995_SPDEF.bed.gz	tf	MCF-7	SPDEF	none	GSE41995	MCF-7,SPDEF,none,GFPtagged,GSE41995
GSM1187119_s04_MCF7_SPDEF_rep1_n.tf	tf	MCF-7	SPDEF	none	GSM1187119	MCF-7,SPDEF,none,rep1,GSM1187119
GSM1187120_s05_MCF7_SPDEF_rep2_n.tf	tf	MCF-7	SPDEF	none	GSM1187120	MCF-7,SPDEF,none,rep2,GSM1187120
GSM1187121_s06_MCF7_SPDEF_rep3_n.tf	tf	MCF-7	SPDEF	none	GSM1187121	MCF-7,SPDEF,none,rep3,GSM1187121
GSM1038226_SRC3inERacells.bed.gz	tf	MCF-7	SRC3	E2	GSM1038226	MCF-7,SRC3,E2,ERa.cells,GSM1038226
GSM1038227_SRC3inERabcells.bed.gz	tf	MCF-7	SRC3	E2	GSM1038227	MCF-7,SRC3,E2,ERab.cells,GSM1038227
GSM1038228_SRC3inERbcells.bed.gz	tf	MCF-7	SRC3	E2	GSM1038228	MCF-7,SRC3,E2,ERb.cells,GSM1038228
ENCF001UNR.bed.gz	tf	MCF-7	SRF	none	ENCF001UNR	MCF-7,SRF,none,rep1,ENCF001UNR
ENCF001UNS.bed.gz	tf	MCF-7	SRF	none	ENCF001UNS	MCF-7,SRF,none,rep2,ENCF001UNS
ENCF001VQD.bed.gz	tf	MCF_10A	STAT3	afimoxifene	ENCF001VQD	MCF_10A,STAT3,afimoxifene,x,ENCF001VQD
ENCF0002CZH.bed.gz	tf	MCF_10A	STAT3	afimoxifene	ENCF0002CZH	MCF_10A,STAT3,afimoxifene,x,ENCF0002CZH
ENCF001VQA.bed.gz	tf	MCF_10A	STAT3	ethanol	ENCF001VQA	MCF_10A,STAT3,ethanol,x,ENCF001VQA
ENCF0002CZE.bed.gz	tf	MCF_10A	STAT3	ethanol	ENCF0002CZE	MCF_10A,STAT3,ethanol,x,ENCF0002CZE
ENCF0002CZG.bed.gz	tf	MCF_10A	STAT3	ethanol	ENCF0002CZG	MCF_10A,STAT3,ethanol,x,ENCF0002CZG
ENCF0002CZF.bed.gz	tf	MCF_10A	STAT3	ethanol	ENCF0002CZF	MCF_10A,STAT3,ethanol,x,ENCF0002CZF
ENCF001VQE.bed.gz	tf	MCF_10A	STAT3	afimoxifene	ENCF001VQE	MCF_10A,STAT3,afimoxifene,x,ENCF001VQE
ENCF0002CZI.bed.gz	tf	MCF_10A	STAT3	afimoxifene	ENCF0002CZI	MCF_10A,STAT3,afimoxifene,x,ENCF0002CZI
ENCF001UNT.bed.gz	tf	MCF-7	TAF1	none	ENCF001UNT	MCF-7,TAF1,none,rep1,ENCF001UNT
ENCF001UNU.bed.gz	tf	MCF-7	TAF1	none	ENCF001UNU	MCF-7,TAF1,none,rep2,ENCF001UNU
GSE66081_MDA-MB-231_TAZ_IDR_0.01.tf	tf	MDA-MB-231	TAZ	none	GSE66081	MDA-MB-231,TAZ,none,x,GSE66081
ENCF001UNV.bed.gz	tf	MCF-7	TCF12	none	ENCF001UNV	MCF-7,TCF12,none,rep1,ENCF001UNV
ENCF001UNW.bed.gz	tf	MCF-7	TCF12	none	ENCF001UNW	MCF-7,TCF12,none,rep2,ENCF001UNW
ENCF001VQI.bed.gz	tf	MCF-7	TCF7L2	none	ENCF001VQI	MCF-7,TCF7L2,none,x,ENCF001VQI
ENCF0002CZM.bed.gz	tf	MCF-7	TCF7L2	none	ENCF0002CZM	MCF-7,TCF7L2,none,x,ENCF0002CZM
GSM1099032_TCF7L2-DHT-peak.bed.gz	tf	MDA-MB-453	TCF7L2	DHT	GSM1099032	MDA-MB-453,TCF7L2,DHT,x,GSM1099032
GSM1099033_TCF7L2-vehicle-peak.bed.g.tf	tf	MDA-MB-453	TCF7L2	vehicle	GSM1099033	MDA-MB-453,TCF7L2,vehicle,x,GSM1099033
ENCF001UNX.bed.gz	tf	MCF-7	TEAD4	none	ENCF001UNX	MCF-7,TEAD4,none,rep1,ENCF001UNX
ENCF001UNY.bed.gz	tf	MCF-7	TEAD4	none	ENCF001UNY	MCF-7,TEAD4,none,rep2,ENCF001UNY
GSE66081_MDA-MB-231_TEAD4_IDR_0.01.tf	tf	MDA-MB-231	TEAD4	none	GSE66081	MDA-MB-231,TEAD4,none,x,GSE66081
GSE41995_THRA.bed.gz	tf	MCF-7	THRA	none	GSE41995	MCF-7,THRA,none,GFPtagged,GSE41995
GSE66753_MACS_peaks_minus_est.bed.tf	tf	MCF-7	TOP2B	minus_estrogen	GSE66753	MCF-7,TOP2B,minus_estrogen,x,GSE66753
GSE66753_MACS_peaks_plus_est.bed.gz.tf	tf	MCF-7	TOP2B	plus_estrogen	GSE66753	MCF-7,TOP2B,plus_estrogen,x,GSE66753
GSE41995_VDR.bed.gz	tf	MCF-7	VDR	none	GSE41995	MCF-7,VDR,none,GFPtagged,GSE41995
GSE41995_XBP1.bed.gz	tf	MCF-7	XBP1	none	GSE41995	MCF-7,XBP1,none,GFPtagged,GSE41995
GSE66081_MDA-MB-231_YAP_IDR_0.01.tf	tf	MDA-MB-231	YAP	none	GSE66081	MDA-MB-231,YAP,none,x,GSE66081
ENCF001VQJ.bed.gz	tf	MCF-7	ZNF217	none	ENCF001VQJ	MCF-7,ZNF217,none,x,ENCF001VQJ
ENCF0002CZN.bed.gz	tf	MCF-7	ZNF217	none	ENCF0002CZN	MCF-7,ZNF217,none,x,ENCF0002CZN
ENCF001SXB.bed.gz	histone	mammary_epithe	H3K4me3	none	ENCF001SXB	mammary_epithelial_cell,H3K4me3,none,x,ENCF001SXB
ENCF001XHB.bed.gz	histone	MCF-7	H3K4me3	none	ENCF001XHB	MCF-7,H3K4me3,none,rep2,ENCF001XHB
ENCF001XHC.bed.gz	histone	MCF-7	H3K4me3	none	ENCF001XHC	MCF-7,H3K4me3,none,rep2,ENCF001XHC
ENCF001XHD.bed.gz	histone	MCF-7	H3K4me3	none	ENCF001XHD	MCF-7,H3K4me3,none,rep1,ENCF001XHD
ENCF001XHE.bed.gz	histone	MCF-7	H3K4me3	none	ENCF001XHE	MCF-7,H3K4me3,none,rep1,ENCF001XHE
ENCF001XDR.bed.gz	histone	mammary_epithe	H3K4me3	none	ENCF001XDR	mammary_epithelial_cell,H3K4me3,none,rep1,ENCF001XDR
ENCF001XDS.bed.gz	histone	mammary_epithe	H3K4me3	none	ENCF001XDS	mammary_epithelial_cell,H3K4me3,none,rep2,ENCF001XDS
ENCF001XDT.bed.gz	histone	mammary_epithe	H3K4me3	none	ENCF001XDT	mammary_epithelial_cell,H3K4me3,none,rep1,ENCF001XDT
ENCF001XDU.bed.gz	histone	mammary_epithe	H3K4me3	none	ENCF001XDU	mammary_epithelial_cell,H3K4me3,none,rep2,ENCF001XDU
GSE49651_MDAMB231.H3K4me3.hg19.A.histone	histone	MDA-MB-231	H3K4me3	none	GSE49651	MDA-MB-231,H3K4me3,none,x,GSE49651
GSM1122656_H3K4me3-MCF7-hg19-sd-q.histone	histone	MCF-7	H3K4me3	none	GSM1122656	MCF-7,H3K4me3,none,x,GSM1122656
GSM1122657_H3K4me3-siJarid1b-MCF7-histone	histone	MCF-7	H3K4me3	siJarid1b	GSM1122657	MCF-7,H3K4me3,siJarid1b,x,GSM1122657
GSM1122666_H3K4me3-SUM159-hg19-sc.histone	histone	SUM159	H3K4me3	none	GSM1122666	SUM159,H3K4me3,none,x,GSM1122666
GSM1402463_H3K4me3-HCC2157-hg19_histone	histone	HCC2157	H3K4me3	none	GSM1402463	HCC2157,H3K4me3,none,x,GSM1402463
GSE42617_H3K4ME3.bed.gz	histone	MCF-7	H3K4me3	none	GSE42617	MCF-7,H3K4me3,none,x,GSE42617
E027-H3K4me3.narrowPeak.gz	histone	BRST.MYOEP	H3K4me3	none	RM_E027-H3K4me3	BRST.MYOEP,H3K4me3,none,x,RM_E027-H3K4me3
E028-H3K4me3.narrowPeak.gz	histone	BRST.HMEC	H3K4me3	none	RM_E028-H3K4me3	BRST.HMEC,H3K4me3,none,x,RM_E028-H3K4me3
E119-H3K4me3.narrowPeak.gz	histone	BRST.vHMEC	H3K4me3	none	RM_E119-H3K4me3	BRST.vHMEC,H3K4me3,none,x,RM_E119-H3K4me3
E027-H3K9ac.narrowPeak.gz	histone	BRST.MYOEP	H3K9ac	none	RM_E027-H3K9ac	BRST.MYOEP,H3K9ac,none,x,RM_E027-H3K9ac
E119-H3K9ac.narrowPeak.gz	histone	BRST.vHMEC	H3K9ac	none	RM_E119-H3K9ac	BRST.vHMEC,H3K9ac,none,x,RM_E119-H3K9ac
ENCF001XRP.bed.gz	tf	fibroblast_of_mar	CTCF	none	ENCF001XRP	fibroblast_of_mammary_gland,CTCF,none,rep1,ENCF001XRP
ENCF001XRQ.bed.gz	tf	fibroblast_of_mar	CTCF	none	ENCF001XRQ	fibroblast_of_mammary_gland,CTCF,none,rep2,ENCF001XRQ
ENCF001XRR.bed.gz	tf	fibroblast_of_mar	CTCF	none	ENCF001XRR	fibroblast_of_mammary_gland,CTCF,none,rep1,ENCF001XRR
ENCF001XRS.bed.gz	tf	fibroblast_of_mar	CTCF	none	ENCF001XRS	fibroblast_of_mammary_gland,CTCF,none,rep2,ENCF001XRS
ENCF0002DDC.bed.gz	tf	fibroblast_of_mar	CTCF	none	ENCF0002DDC	fibroblast_of_mammary_gland,CTCF,none,x,ENCF0002DDC
ENCF001XDV.bed.gz	histone	fibroblast_of_mar	H3K4me3	none	ENCF001XDV	fibroblast_of_mammary_gland,H3K4me3,none,rep1,ENCF001XDV
ENCF001XDW.bed.gz	histone	fibroblast_of_mar	H3K4me3	none	ENCF001XDW	fibroblast_of_mammary_gland,H3K4me3,none,rep2,ENCF001XDW
ENCF001XDX.bed.gz	histone	fibroblast_of_mar	H3K4me3	none	ENCF001XDX	fibroblast_of_mammary_gland,H3K4me3,none,rep1,ENCF001XDX
ENCF001XDY.bed.gz	histone	fibroblast_of_mar	H3K4me3	none	ENCF001XDY	fibroblast_of_mammary_gland,H3K4me3,none,rep2,ENCF001XDY
ENCF001VQH.bed.gz	tf	MCF-7	HA-E2F1	none	ENCF001VQH	MCF-7,HA-E2F1,none,x,ENCF001VQH
ENCF0002CZL.bed.gz	tf	MCF-7	HA-E2F1	none	ENCF0002CZL	MCF-7,HA-E2F1,none,x,ENCF0002CZL
GSM2037451_HAUSP_H1299_CHIP_peal.tf	tf	H1299	HAUSP	none	GSM2037451	H1299,HAUSP,none,x,GSM2037451
GSM2037452_H1299_HIF_hg19_rmdup_p.tf	tf	H1299	HIF	none	GSM2037452	H1299,HIF,none,x,GSM2037452
wgEncodeAwgDnaseUwHmUniPkn.narrowf.dnase	HMF	open-chrom	none	x	ENC_dnase	HMF,open-chrom,none,x,ENC_dnase

**Supplementary Table 7: Associations for ten novel and ten previously reported (and replicated)
ER-negative breast cancer susceptibility loci, by ER status (BCAC data only)**

SNP	Location	ER-negative [†]		ER-positive [‡]		Heterogeneity P-value*
		OR (95%CI)	P-value	OR (95%CI)	P-value	
Loci identified by the present study						
rs200648189	2p23.3	0.94 (0.91-0.97)	4.7x10 ⁻⁴	0.99 (0.97-1.01)	0.49	4.7x10 ⁻³
rs6569648	6q23.1	0.93 (0.90-0.95)	4.3x10 ⁻⁸	0.96 (0.94-0.97)	2.0x10 ⁻⁷	2.5x10 ⁻²
rs66823261	8p23.3	1.09 (1.06-1.12)	5.6x10 ⁻⁹	1.02 (1.01-1.04)	9.6x10 ⁻³	1.3x10 ⁻⁵
rs17350191	8q24.13	1.07 (1.04-1.09)	2.0x10 ⁻⁸	1.03 (1.02-1.05)	6.3x10 ⁻⁵	1.1x10 ⁻³
rs11374964	11q22.3	0.94 (0.92-0.96)	3.6x10 ⁻⁸	1.02 (1.01-1.04)	5.9x10 ⁻³	2.8x10 ⁻¹²
rs74911261	11q22.3	0.82 (0.75-0.89)	2.3x10 ⁻⁶	1.05 (1.00-1.10)	5.0x10 ⁻²	5.7x10 ⁻⁹
rs11076805	16p13.3	0.92 (0.90-0.95)	2.2x10 ⁻⁸	0.98 (0.97-1.00)	4.9x10 ⁻²	1.2x10 ⁻⁴
rs36194942	18q12.1	0.94 (0.91-0.96)	2.5x10 ⁻⁷	0.98 (0.96-0.99)	2.9x10 ⁻³	2.0x10 ⁻³
rs322144	19p13.2	0.95 (0.93-0.97)	2.4x10 ⁻⁵	0.98 (0.96-1.00)	1.2x10 ⁻²	0.12
rs113701136	19q12	1.07 (1.04-1.09)	1.7x10 ⁻⁷	1.02 (1.00-1.04)	1.6x10 ⁻²	9.8x10 ⁻⁴
Previously reported loci (associations replicated by the present study)						
rs6678914	1q32.1	0.92 (0.90-0.94)	2.6x10 ⁻¹²	1.02 (1.00-1.03)	2.4x10 ⁻²	8.1x10 ⁻¹⁶
rs4245739	1q32.1	1.14 (1.11-1.16)	3.1x10 ⁻²³	1.00 (0.98-1.02)	0.87	5.0x10 ⁻¹⁹
rs12710696	2p24.1	1.06 (1.04-1.09)	6.5x10 ⁻⁸	1.01 (1.00-1.03)	7.7x10 ⁻²	1.3x10 ⁻⁴
rs4577244	2p23.2	0.92 (0.90-0.95)	1.5x10 ⁻⁹	1.02 (1.01-1.04)	1.1x10 ⁻²	2.8x10 ⁻¹⁴
rs10069690	5p15.33	1.18 (1.15-1.21)	1.5x10 ⁻³⁵	1.03 (1.01-1.04)	1.1x10 ⁻³	7.3x10 ⁻²⁵
rs3757322	6q25.1	1.15 (1.12-1.18)	2.8x10 ⁻³¹	1.07 (1.05-1.08)	5.4x10 ⁻¹⁷	1.1x10 ⁻⁹
rs2747652	6q25.2	0.91 (0.89-0.93)	1.9x10 ⁻¹⁸	0.95 (0.93-0.96)	1.5x10 ⁻¹³	3.0x10 ⁻⁵
rs6562760	13q22.1	0.92 (0.90-0.95)	8.7x10 ⁻¹⁰	0.96 (0.94-0.98)	2.3x10 ⁻⁶	2.7x10 ⁻³
rs11075995	16q12.2	1.09 (1.06-1.12)	1.0x10 ⁻¹⁰	1.02 (1.00-1.04)	2.2x10 ⁻²	4.2x10 ⁻⁶
rs67397200	19p13.11	1.17 (1.14-1.19)	2.7x10 ⁻³⁷	0.99 (0.98-1.01)	0.52	6.7x10 ⁻³⁶

[†] Combined Breast Cancer Association Consortium (BCAC) data from 16,988 cases and 87,962 controls

[‡] Combined BCAC data from 65,275 cases and 87,962 controls

*ER-negative case-only analysis of BCAC data (N=82,263), by ER status

OR, odds ratio per copy of the minor allele; CI, confidence interval

Supplementary Table 8: Associations for ten novel and ten previously reported (and replicated)

ER-negative breast cancer susceptibility loci, by age in years (BCAC data only)[†]

SNP	Location	OR (95%CI)				Heterogeneity P-value*
		< 40	40-49	50-59	≥ 60	
Loci identified by the present study						
rs200648189	2p23.3	0.98 (0.9-1.07)	0.96 (0.9-1.03)	0.94 (0.89-1.01)	0.93 (0.87-0.98)	0.060
rs6569648	6q23.1	0.93 (0.87-1.00)	0.91 (0.86-0.96)	0.95 (0.90-1.00)	0.95 (0.91-1.00)	0.16
rs66823261	8p23.3	1.16 (1.08-1.25)	1.15 (1.08-1.22)	1.11 (1.05-1.17)	1.06 (1.01-1.11)	0.15
rs17350191	8q24.13	1.09 (1.03-1.16)	1.08 (1.03-1.13)	1.05 (1.01-1.10)	1.09 (1.04-1.13)	0.84
rs11374964	11q22.3	0.89 (0.83-0.94)	0.93 (0.89-0.98)	0.95 (0.91-0.99)	0.95 (0.91-0.99)	0.16
rs74911261	11q22.3	0.72 (0.57-0.91)	0.78 (0.65-0.93)	0.86 (0.74-1.01)	0.83 (0.72-0.96)	0.12
rs11076805	16p13.3	0.92 (0.85-0.99)	0.95 (0.9-1.01)	0.92 (0.87-0.97)	0.93 (0.88-0.97)	0.68
rs36194942	18q12.1	0.95 (0.89-1.01)	0.92 (0.87-0.97)	0.94 (0.90-0.99)	0.93 (0.89-0.97)	0.95
rs322144	19p13.2	0.97 (0.91-1.04)	0.96 (0.91-1.02)	0.93 (0.89-0.98)	0.95 (0.91-1.00)	0.98
rs113701136	19q12	1.06 (1.00-1.13)	1.05 (1.00-1.11)	1.10 (1.05-1.15)	1.06 (1.02-1.11)	0.33
Previously reported loci (associations replicated by the present study)						
rs6678914	1q32.1	0.95 (0.89-1.00)	0.97 (0.92-1.01)	0.92 (0.88-0.96)	0.92 (0.88-0.96)	0.28
rs4245739	1q32.1	1.15 (1.08-1.23)	1.11 (1.06-1.17)	1.16 (1.11-1.21)	1.12 (1.07-1.17)	0.63
rs12710696	2p24.1	1.05 (0.99-1.12)	1.10 (1.05-1.16)	1.05 (1.01-1.10)	1.06 (1.02-1.11)	0.62
rs4577244	2p23.2	0.87 (0.81-0.94)	0.96 (0.90-1.01)	0.93 (0.89-0.98)	0.90 (0.86-0.95)	0.65
rs10069690	5p15.33	1.25 (1.17-1.34)	1.20 (1.14-1.27)	1.20 (1.15-1.26)	1.10 (1.06-1.15)	1.2x10 ⁻³
rs3757322	6q25.1	1.21 (1.14-1.29)	1.18 (1.13-1.24)	1.16 (1.11-1.21)	1.12 (1.08-1.17)	0.065
rs2747652	6q25.2	0.97 (0.91-1.03)	0.91 (0.87-0.96)	0.87 (0.83-0.91)	0.90 (0.87-0.94)	1.0x10 ⁻²
rs6562760	13q22.1	0.92 (0.86-0.99)	0.87 (0.82-0.92)	0.93 (0.89-0.98)	0.95 (0.91-1.00)	0.052
rs11075995	16q12.2	1.12 (1.04-1.20)	1.08 (1.02-1.14)	1.06 (1.01-1.11)	1.08 (1.04-1.13)	0.75
rs67397200	19p13.11	1.26 (1.18-1.34)	1.18 (1.13-1.25)	1.14 (1.09-1.19)	1.14 (1.10-1.19)	3.8x10 ⁻²

[†]Combined Breast Cancer Association Consortium (BCAC) data from 1954, 3487, 4179 and 5116 cases aged <40, 40-49, 50-59 and ≥60 years, respectively, and 82,347 controls; *ER-negative case-only analysis, by age (trend test, 1df)

OR, odds ratio per copy of the minor allele; CI, confidence interval

Supplementary Table 9: Novel overall breast cancer susceptibility loci from Michailidou et al. (2017)*: asso

Location	SNP†	Chr	Position	Alleles‡	MAF	GWAS	
						OR (95%CI)	P-value
1p36.13	rs2992756	1	18807339	C/T	0.49	0.99 (0.93-1.04)	5.8x10 ⁻⁰¹
1p34.2	rs4233486	1	41380440	T/C	0.36	0.97 (0.92-1.03)	3.2x10 ⁻⁰¹
1p34.2	rs79724016	1	42137311	T/G	0.03	0.95 (0.81-1.11)	5.2x10 ⁻⁰¹
1p34.1	rs1707302	1	46600917	G/A	0.34	1.01 (0.96-1.07)	6.9x10 ⁻⁰¹
1p32.3	rs140850326	1	50846032	I/D¥	0.49	0.93 (0.87-0.99)	3.4x10 ⁻⁰²
1p22.3	rs17426269	1	88156923	G/A	0.15	0.99 (0.92-1.07)	8.2x10 ⁻⁰¹
1p12	rs7529522	1	118230221	T/C	0.23	1.04 (0.97-1.11)	2.9x10 ⁻⁰¹
1q22	rs4971059	1	155148781	G/A	0.35	1.03 (0.97-1.09)	3.6x10 ⁻⁰¹
1q32.1	rs35383942	1	201437832	C/T	0.06	1.00 (0.88-1.15)	9.8x10 ⁻⁰¹
1q41	rs11117758	1	217220574	G/A	0.21	0.92 (0.86-0.99)	1.7x10 ⁻⁰²
2p25.1	rs113577745	2	10135681	C/G	0.10	1.07 (0.98-1.17)	1.3x10 ⁻⁰¹
2q13	rs71801447	2	111925731	CTTATGTT/C	0.06	1.11 (0.97-1.26)	1.4x10 ⁻⁰¹
2q36.3	rs12479355	2	227226952	A/G	0.21	0.93 (0.87-1.00)	3.8x10 ⁻⁰²
3p13	rs6805189	3	71532113	T/C	0.48	0.97 (0.92-1.03)	3.2x10 ⁻⁰¹
3p12.1	rs13066793	3	87037543	A/G	0.09	0.93 (0.82-1.07)	3.2x10 ⁻⁰¹
3p12.1	rs9833888	3	99723580	G/T	0.22	1.02 (0.96-1.09)	4.9x10 ⁻⁰¹
3q23	rs34207738	3	141112859	CTT/C	0.41	0.99 (0.93-1.06)	8.7x10 ⁻⁰¹
3q26.31	rs58058861	3	172285237	G/A	0.21	1.02 (0.96-1.09)	4.8x10 ⁻⁰¹
4p14	rs6815814	4	38816338	A/C	0.26	1.03 (0.97-1.09)	3.9x10 ⁻⁰¹
4q21.23	4:84370124	4	84370124	TA/TAA	0.47	1.06 (0.99-1.13)	1.1x10 ⁻⁰¹
4q22.1	rs10022462	4	89243818	C/T	0.44	1.04 (0.99-1.10)	1.3x10 ⁻⁰¹
4q28.1	rs77528541	4	126843504	G/T	0.13	0.91 (0.83-0.99)	2.3x10 ⁻⁰²
5p15.33	rs116095464	5	345109	T/C	0.05	1.13 (1.01-1.27)	3.5x10 ⁻⁰²
5q11.1	rs72749841	5	49641645	T/C	0.16	0.94 (0.84-1.06)	3.2x10 ⁻⁰¹
5q11.1	rs35951924	5	50195093	A/AT	0.32	0.99 (0.92-1.07)	8.2x10 ⁻⁰¹
5q22.1	rs6882649	5	111217786	T/G	0.34	0.93 (0.87-0.98)	8.1x10 ⁻⁰³
5q31.1	rs6596100	5	132407058	C/T	0.25	1.01 (0.95-1.07)	7.7x10 ⁻⁰¹
5q35.1	rs4562056	5	169591487	G/T	0.33	1.03 (0.98-1.10)	2.6x10 ⁻⁰¹
6p22.3	rs3819405	6	16399557	C/T	0.33	0.96 (0.90-1.02)	2.2x10 ⁻⁰¹
6p22.3	rs2223621	6	20621238	C/T	0.38	1.04 (0.99-1.10)	1.5x10 ⁻⁰¹
6p22.2	rs71557345	6	26680698	G/A	0.07	0.94 (0.85-1.05)	2.9x10 ⁻⁰¹
6q14.1	rs12207986	6	81094287	A/G	0.47	0.94 (0.89-0.99)	1.7x10 ⁻⁰²
7p15.3	rs7971	7	21940960	A/G	0.35	1.03 (0.97-1.08)	3.8x10 ⁻⁰¹
7p15.1	rs17156577	7	28356889	T/C	0.11	1.15 (1.04-1.27)	5.3x10 ⁻⁰³
7q21.3	rs17268829	7	94113799	T/C	0.28	1.05 (0.99-1.11)	1.2x10 ⁻⁰¹
7q22.1	rs71559437	7	101552440	G/A	0.12	0.97 (0.90-1.06)	5.0x10 ⁻⁰¹
8q22.3	rs514192	8	102478959	T/A	0.32	1.04 (0.98-1.10)	1.8x10 ⁻⁰¹
8q23.1	rs12546444	8	106358620	A/T	0.10	0.97 (0.89-1.07)	5.9x10 ⁻⁰¹
9q33.1	rs1895062	9	119313486	A/G	0.41	1.00 (0.94-1.05)	9.0x10 ⁻⁰¹
9q33.3	rs10760444	9	129396434	A/G	0.43	1.07 (1.02-1.13)	1.3x10 ⁻⁰²
9q34.2	rs587745765	9	136151579	I/D‡	0.20	1.09 (1.00-1.18)	5.1x10 ⁻⁰²
10p14	rs67958007	10	9088113	TG/T	0.12	1.04 (0.94-1.15)	4.3x10 ⁻⁰¹
10q23.33	rs140936696	10	95292187	C/CAA	0.18	1.02 (0.93-1.11)	7.2x10 ⁻⁰¹
11p15	rs6597981	11	803017	G/A	0.48	0.96 (0.91-1.02)	1.7x10 ⁻⁰¹

12q21.31	12:85009437:T:C	12	85009437	T/C	0.34	0.99 (0.93-1.05)	7.2x10 ⁻⁰¹
12q24.31	12:120832146:C:T	12	120832146	C/T	0.16	1.06 (0.98-1.15)	1.6x10 ⁻⁰¹
14q32.33	rs10623258	14	105212261	C/CTT	0.45	1.01 (0.93-1.10)	8.1x10 ⁻⁰¹
16q12.2	rs28539243	16	54682064	G/A	0.49	1.06 (1.00-1.12)	3.4x10 ⁻⁰²
16q13	rs2432539	16	56420987	G/A	0.40	1.03 (0.97-1.08)	3.5x10 ⁻⁰¹
16q24.2	rs4496150	16	87085237	C/A	0.25	0.93 (0.87-0.99)	1.7x10 ⁻⁰²
17q21.2	rs72826962	17	40836389	C/T	0.01	0.86 (0.58-1.26)	4.3x10 ⁻⁰¹
17q21.31	17:44252468:G:A	17	44252468	G/A	0.19	0.94 (0.87-1.01)	1.1x10 ⁻⁰¹
18q12.1	rs117618124	18	29977689	T/C	0.05	0.88 (0.77-1.01)	7.2x10 ⁻⁰²
19p13.13	rs78269692	19	13158277	T/C	0.05	1.08 (0.95-1.23)	2.3x10 ⁻⁰¹
19p13.12	rs2594714	19	13954571	G/A	0.23	0.97 (0.91-1.03)	3.4x10 ⁻⁰¹
19p13.11	rs2965183	19	19545696	G/A	0.35	1.03 (0.98-1.09)	2.4x10 ⁻⁰¹
19q13.22	rs71338792	19	46183031	A/AT	0.23	1.02 (0.94-1.11)	6.0x10 ⁻⁰¹
20p12.3	rs16991615	20	5948227	G/A	0.06	1.15 (1.03-1.29)	1.4x10 ⁻⁰²
20q13.13	rs6122906	20	48945911	A/G	0.18	1.07 (1.00-1.14)	6.8x10 ⁻⁰²
22q13.1	rs738321	22	38568833	C/G	0.38	0.97 (0.92-1.02)	2.8x10 ⁻⁰¹
22q13.2	rs73161324	22	42038786	C/T	0.06	1.19 (1.03-1.36)	1.7x10 ⁻⁰²
22q13.31	rs28512361	22	46283297	G/A	0.11	1.01 (0.90-1.13)	9.2x10 ⁻⁰¹

*Michailidou, K. et al. Identification of more than 70 new breast cancer susceptibility loci for breast cancer and definiti

[†]Results for 2p23.3-rs6725517, 6q23.1-rs6569648 and 8q24.13-rs58847541 are not reported because they represent the Chr, chromosome; MAF, minor allele frequency; BCAC, Breast Cancer Association Consortium; CIMBA, Consortium of In

[‡]21 base-pair deletion; [§]36 base-pair deletion
BCAC results were based on GWAS data for 4,480 cases and 12,632 controls, iCOGS data for 7,333 cases and 42,468 con
CIMBA results were based on data for 18,908 *BRCA1* mutation carriers (9,414 with breast cancer)

Associations observed with ER-negative breast cancer based on P<0.05 in meta-analysis of all BCAC data

Associations observed with breast cancer for *BRCA1* mutation carriers based on P<0.05 in meta-analysis of

ciations with risk of ER-negative breast cancer and breast cancer for *BRCA1* mutation carriers

ER-negative breast cancer (BCAC)					<i>BRCA1</i> mutation
iCOGS		OncoArray		Combined	All CIMBA data co
OR (95%CI)	P-value	OR (95%CI)	P-value	P-value	HR (95%CI)
1.01 (0.97-1.06)	4.8x10 ⁻⁰¹	1.03 (1.00-1.07)	4.2x10 ⁻⁰²	1.1x10 ⁻⁰¹	1.01 (0.97-1.04)
0.95 (0.91-1.00)	4.7x10 ⁻⁰²	0.97 (0.94-1.00)	6.6x10 ⁻⁰²	4.4x10 ⁻⁰³	0.95 (0.92-0.99)
0.92 (0.83-1.03)	1.4x10 ⁻⁰¹	0.89 (0.98-1.07)	6.2x10 ⁻⁰¹	1.4x10 ⁻⁰¹	0.96 (0.87-1.06)
1.00 (0.96-1.04)	8.8x10 ⁻⁰¹	1.01 (0.98-1.04)	5.4x10 ⁻⁰¹	5.7x10 ⁻⁰¹	0.99 (0.95-1.03)
0.98 (0.94-1.02)	3.1x10 ⁻⁰¹	0.96 (0.93-0.99)	2.3x10 ⁻⁰²	2.9x10 ⁻⁰³	1.03 (0.99-1.06)
1.00 (0.95-1.05)	9.6x10 ⁻⁰¹	1.04 (0.99-1.08)	1.2x10 ⁻⁰¹	3.4x10 ⁻⁰¹	1.04 (0.99-1.09)
1.07 (1.02-1.11)	4.0x10 ⁻⁰³	1.05 (1.02-1.09)	5.8x10 ⁻⁰³	4.8x10 ⁻⁰⁵	1.03 (0.99-1.08)
0.97 (0.94-1.01)	1.6x10 ⁻⁰¹	1.03 (1.00-1.07)	5.7x10 ⁻⁰²	4.2x10 ⁻⁰¹	0.99 (0.96-1.03)
1.05 (0.96-1.14)	3.0x10 ⁻⁰¹	1.15 (1.08-1.23)	3.2x10 ⁻⁰⁵	3.3x10 ⁻⁰⁴	1.02 (0.94-1.10)
1.03 (0.98-1.08)	1.9x10 ⁻⁰¹	0.98 (0.95-1.02)	3.9x10 ⁻⁰¹	3.7x10 ⁻⁰¹	0.94 (0.90-0.98)
1.02 (0.96-1.09)	5.1x10 ⁻⁰¹	1.06 (1.01-1.12)	1.8x10 ⁻⁰²	7.4x10 ⁻⁰³	0.99 (0.94-1.05)
1.04 (0.96-1.13)	3.0x10 ⁻⁰¹	1.05 (0.99-1.12)	1.2x10 ⁻⁰¹	3.2x10 ⁻⁰²	1.01 (0.94-1.09)
1.01 (0.96-1.05)	8.1x10 ⁻⁰¹	1.00 (0.96-1.04)	9.8x10 ⁻⁰¹	4.3x10 ⁻⁰¹	0.96 (0.92-1.01)
0.94 (0.90-0.97)	8.9x10 ⁻⁰⁴	1.00 (0.97-1.03)	8.6x10 ⁻⁰¹	9.9x10 ⁻⁰³	0.97 (0.93-1.00)
0.95 (0.89-1.01)	1.2x10 ⁻⁰¹	0.96 (0.91-1.02)	1.8x10 ⁻⁰¹	2.4x10 ⁻⁰²	0.96 (0.90-1.02)
1.01 (0.97-1.06)	6.2x10 ⁻⁰¹	1.01 (0.98-1.05)	5.1x10 ⁻⁰¹	2.5x10 ⁻⁰¹	1.00 (0.96-1.04)
1.01 (0.97-1.05)	6.6x10 ⁻⁰¹	1.03 (1.00-1.07)	5.5x10 ⁻⁰²	1.1x10 ⁻⁰¹	1.03 (0.99-1.07)
0.99 (0.94-1.03)	5.3x10 ⁻⁰¹	1.00 (0.96-1.04)	9.5x10 ⁻⁰¹	8.5x10 ⁻⁰¹	0.98 (0.94-1.03)
1.01 (0.97-1.06)	5.3x10 ⁻⁰¹	1.06 (1.02-1.10)	2.9x10 ⁻⁰³	4.9x10 ⁻⁰³	0.99 (0.95-1.03)
1.08 (1.04-1.13)	3.9x10 ⁻⁰⁵	1.03 (1.00-1.06)	7.9x10 ⁻⁰²	2.9x10 ⁻⁰⁵	0.99 (0.96-1.03)
1.04 (1.00-1.08)	5.3x10 ⁻⁰²	1.01 (0.98-1.05)	4.2x10 ⁻⁰¹	2.3x10 ⁻⁰²	0.98 (0.94-1.01)
0.92 (0.87-0.98)	6.9x10 ⁻⁰³	0.94 (0.90-0.99)	1.4x10 ⁻⁰²	1.3x10 ⁻⁰⁵	1.03 (0.97-1.09)
1.15 (1.06-1.25)	5.8x10 ⁻⁰⁴	1.03 (0.96-1.11)	3.5x10 ⁻⁰¹	5.2x10 ⁻⁰⁴	1.01 (0.93-1.09)
0.91 (0.84-0.99)	2.1x10 ⁻⁰²	0.99 (0.94-1.04)	6.5x10 ⁻⁰¹	5.2x10 ⁻⁰²	0.99 (0.93-1.05)
0.97 (0.93-1.02)	2.0x10 ⁻⁰¹	0.96 (0.93-1.00)	4.4x10 ⁻⁰²	1.5x10 ⁻⁰²	1.00 (0.96-1.04)
0.98 (0.94-1.02)	3.0x10 ⁻⁰¹	0.98 (0.94-1.01)	1.7x10 ⁻⁰¹	7.9x10 ⁻⁰³	0.99 (0.95-1.03)
1.01 (0.96-1.06)	6.6x10 ⁻⁰¹	0.95 (0.92-0.99)	8.4x10 ⁻⁰³	1.2x10 ⁻⁰¹	0.97 (0.93-1.01)
1.03 (0.99-1.07)	2.1x10 ⁻⁰¹	1.02 (0.99-1.05)	2.8x10 ⁻⁰¹	5.9x10 ⁻⁰²	0.98 (0.95-1.02)
0.99 (0.95-1.04)	8.3x10 ⁻⁰¹	0.97 (0.94-1.00)	5.4x10 ⁻⁰²	3.5x10 ⁻⁰²	0.98 (0.94-1.02)
1.00 (0.96-1.04)	8.9x10 ⁻⁰¹	1.02 (0.99-1.05)	2.4x10 ⁻⁰¹	2.1x10 ⁻⁰¹	0.98 (0.95-1.02)
0.98 (0.91-1.06)	6.2x10 ⁻⁰¹	0.91 (0.84-0.98)	1.0x10 ⁻⁰²	1.7x10 ⁻⁰²	1.07 (0.99-1.16)
0.97 (0.94-1.01)	1.5x10 ⁻⁰¹	0.96 (0.93-0.99)	1.8x10 ⁻⁰²	6.1x10 ⁻⁰⁴	0.95 (0.92-0.98)
0.96 (0.92-0.99)	2.7x10 ⁻⁰²	0.96 (0.93-0.99)	2.0x10 ⁻⁰²	8.3x10 ⁻⁰³	1.02 (0.98-1.06)
1.07 (1.01-1.13)	2.5x10 ⁻⁰²	1.05 (1.00-1.10)	5.8x10 ⁻⁰²	3.3x10 ⁻⁰⁴	1.01 (0.95-1.07)
1.02 (0.98-1.06)	3.9x10 ⁻⁰¹	1.02 (0.98-1.05)	4.0x10 ⁻⁰¹	1.0x10 ⁻⁰¹	1.02 (0.98-1.07)
0.96 (0.90-1.02)	2.0x10 ⁻⁰¹	0.95 (0.90-1.00)	3.5x10 ⁻⁰²	1.7x10 ⁻⁰²	0.99 (0.93-1.05)
1.00 (0.97-1.05)	8.2x10 ⁻⁰¹	1.01 (0.98-1.05)	4.2x10 ⁻⁰¹	1.8x10 ⁻⁰¹	1.02 (0.98-1.06)
0.95 (0.89-1.03)	2.0x10 ⁻⁰¹	0.98 (0.93-1.03)	4.4x10 ⁻⁰¹	1.3x10 ⁻⁰¹	0.98 (0.92-1.05)
0.96 (0.92-1.00)	3.1x10 ⁻⁰²	0.93 (0.90-0.96)	7.8x10 ⁻⁰⁶	1.4x10 ⁻⁰⁵	0.95 (0.92-0.99)
1.04 (1.00-1.08)	2.8x10 ⁻⁰²	1.05 (1.02-1.08)	3.0x10 ⁻⁰³	1.4x10 ⁻⁰⁵	1.01 (0.97-1.05)
1.01 (0.96-1.06)	7.2x10 ⁻⁰¹	1.05 (1.01-1.09)	1.3x10 ⁻⁰²	8.0x10 ⁻⁰³	1.02 (0.98-1.07)
1.03 (0.97-1.09)	3.0x10 ⁻⁰¹	1.08 (1.03-1.14)	8.7x10 ⁻⁰⁴	8.4x10 ⁻⁰⁴	0.96 (0.90-1.01)
1.03 (0.98-1.09)	2.3x10 ⁻⁰¹	1.04 (0.99-1.08)	9.7x10 ⁻⁰²	4.0x10 ⁻⁰²	1.00 (0.95-1.05)
0.95 (0.92-0.99)	1.4x10 ⁻⁰²	0.94 (0.91-0.97)	3.8x10 ⁻⁰⁴	9.9x10 ⁻⁰⁶	0.97 (0.94-1.01)

0.96 (0.92-1.01)	9.2x10 ⁻⁰²	0.93 (0.90-0.96)	6.1x10 ⁻⁰⁵	1.1x10 ⁻⁰⁴	1.02 (0.98-1.06)
1.06 (1.00-1.12)	5.1x10 ⁻⁰²	1.04 (1.00-1.09)	5.4x10 ⁻⁰²	2.5x10 ⁻⁰³	1.06 (1.00-1.11)
1.03 (0.99-1.07)	9.4x10 ⁻⁰²	1.03 (1.00-1.06)	6.8x10 ⁻⁰²	1.5x10 ⁻⁰²	1.00 (0.97-1.04)
1.01 (0.98-1.05)	4.8x10 ⁻⁰¹	1.05 (1.01-1.08)	4.1x10 ⁻⁰³	1.1x10 ⁻⁰³	0.97 (0.94-1.01)
1.02 (0.98-1.06)	3.1x10 ⁻⁰¹	1.02 (0.99-1.06)	1.9x10 ⁻⁰¹	5.5x10 ⁻⁰²	0.98 (0.94-1.02)
0.98 (0.94-1.02)	3.8x10 ⁻⁰¹	0.96 (0.92-0.99)	1.9x10 ⁻⁰²	1.7x10 ⁻⁰³	0.97 (0.93-1.01)
1.03 (0.85-1.25)	7.5x10 ⁻⁰¹	1.13 (0.98-1.30)	9.0x10 ⁻⁰²	2.0x10 ⁻⁰¹	1.06 (0.87-1.27)
0.96 (0.91-1.02)	1.6x10 ⁻⁰¹	0.95 (0.91-0.99)	1.3x10 ⁻⁰²	1.7x10 ⁻⁰³	0.99 (0.94-1.04)
0.92 (0.83-1.01)	8.9x10 ⁻⁰²	0.84 (0.77-0.91)	2.7x10 ⁻⁰⁵	5.0x10 ⁻⁰⁶	0.89 (0.81-0.98)
1.05 (0.94-1.17)	4.2x10 ⁻⁰¹	1.09 (1.02-1.17)	1.4x10 ⁻⁰²	6.2x10 ⁻⁰³	1.02 (0.94-1.12)
0.98 (0.93-1.02)	2.8x10 ⁻⁰¹	1.00 (0.96-1.04)	8.7x10 ⁻⁰¹	3.3x10 ⁻⁰¹	1.00 (0.95-1.04)
1.05 (1.01-1.09)	9.3x10 ⁻⁰³	1.05 (1.02-1.09)	2.2x10 ⁻⁰³	2.3x10 ⁻⁰⁵	1.02 (0.98-1.05)
1.03 (0.98-1.09)	3.0x10 ⁻⁰¹	1.03 (0.99-1.07)	1.0x10 ⁻⁰¹	2.3x10 ⁻⁰²	0.99 (0.95-1.04)
1.08 (1.00-1.17)	3.7x10 ⁻⁰²	1.10 (1.04-1.18)	2.2x10 ⁻⁰³	1.7x10 ⁻⁰⁵	0.98 (0.91-1.05)
1.00 (0.95-1.05)	9.2x10 ⁻⁰¹	1.08 (1.03-1.12)	4.5x10 ⁻⁰⁴	2.9x10 ⁻⁰³	0.98 (0.94-1.03)
0.98 (0.95-1.02)	3.7x10 ⁻⁰¹	0.99 (0.96-1.02)	5.7x10 ⁻⁰¹	1.9x10 ⁻⁰¹	1.03 (0.99-1.06)
1.10 (1.01-1.19)	2.5x10 ⁻⁰²	1.10 (1.03-1.18)	2.8x10 ⁻⁰³	1.2x10 ⁻⁰⁵	1.04 (0.96-1.12)
1.12 (1.05-1.21)	1.3x10 ⁻⁰³	1.09 (1.04-1.14)	8.3x10 ⁻⁰⁴	1.5x10 ⁻⁰⁵	1.04 (0.98-1.10)

on of risk-associated genomic features, Reference 1 in the main text

the same signals as those reported for these regions for ER-negative disease

investigators of Modifiers of BRCA1/2; [†]More common allele listed first, minor allele second

controls and OncoArray data 9,655 cases and 45,494 controls

all CIMBA data

carriers
combined
<i>P</i> -value
7.5x10 ⁻⁰¹
1.5x10 ⁻⁰²
4.4x10 ⁻⁰¹
6.9x10 ⁻⁰¹
1.8x10 ⁻⁰¹
1.6x10 ⁻⁰¹
1.6x10 ⁻⁰¹
7.0x10 ⁻⁰¹
7.0x10 ⁻⁰¹
4.6x10 ⁻⁰³
8.0x10 ⁻⁰¹
7.9x10 ⁻⁰¹
1.1x10 ⁻⁰¹
7.8x10 ⁻⁰²
1.7x10 ⁻⁰¹
9.9x10 ⁻⁰¹
1.5x10 ⁻⁰¹
4.1x10 ⁻⁰¹
7.5x10 ⁻⁰¹
7.7x10 ⁻⁰¹
2.0x10 ⁻⁰¹
2.9x10 ⁻⁰¹
8.9x10 ⁻⁰¹
6.4x10 ⁻⁰¹
9.7x10 ⁻⁰¹
4.8x10 ⁻⁰¹
1.7x10 ⁻⁰¹
3.9x10 ⁻⁰¹
3.3x10 ⁻⁰¹
4.0x10 ⁻⁰¹
8.4x10 ⁻⁰²
5.4x10 ⁻⁰³
2.6x10 ⁻⁰¹
7.7x10 ⁻⁰¹
2.8x10 ⁻⁰¹
7.3x10 ⁻⁰¹
4.2x10 ⁻⁰¹
6.0x10 ⁻⁰¹
8.0x10 ⁻⁰³
6.1x10 ⁻⁰¹
3.0x10 ⁻⁰¹
1.0x10 ⁻⁰¹
9.3x10 ⁻⁰¹
1.4x10 ⁻⁰¹

3.4×10^{-01}

3.8×10^{-02}

9.3×10^{-01}

1.7×10^{-01}

2.8×10^{-01}

1.6×10^{-01}

5.7×10^{-01}

6.7×10^{-01}

1.5×10^{-02}

5.9×10^{-01}

8.4×10^{-01}

4.2×10^{-01}

7.3×10^{-01}

6.2×10^{-01}

4.5×10^{-01}

1.8×10^{-01}

3.2×10^{-01}

1.9×10^{-01}

Supplementary Table 10: Other previously reported (non ER-negative disease-specific) breast cancer susceptibility loci: associations with risk of ER-negative breast cancer* and breast cancer for *BRCA1* mutation carr

Location	SNP	Reference	Chr	Position	Alleles [†]	MAF	ER-negative breast cancer (BCAC)						BRCA1 mutation	
							GWAS		iCOGS		OncoArray		P-value	All CIMBA data cc
							OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value		
1p36.22	rs616488	[1]	1	10566215	A/G	0.33	0.91 (0.86-0.96)	7.3x10 ⁻⁰⁴	0.91 (0.87-0.95)	3.9x10 ⁻⁰⁶	0.89 (0.86-0.92)	4.8x10 ⁻¹¹	4.1x10 ⁻¹⁸	0.96 (0.92-1.00)
1p13.2	rs11552449	[1]	1	114448389	C/T	0.17	1.10 (1.02-1.18)	9.4x10 ⁻⁰³	1.04 (0.99-1.10)	8.3x10 ⁻⁰²	1.04 (1.00-1.08)	7.3x10 ⁻⁰²	8.4x10 ⁻⁰⁴	1.02 (0.97-1.07)
1p11.2	rs11249433	[2]	1	121280613	A/G	0.41	0.99 (0.93-1.06)	7.8x10 ⁻⁰¹	1.00 (0.96-1.04)	9.4x10 ⁻⁰¹	1.02 (0.99-1.06)	2.0x10 ⁻⁰¹	3.9x10 ⁻⁰¹	0.99 (0.95-1.03)
1q21.1	rs12405132	[3]	1	145644984	A/C	0.37	0.95 (0.90-1.01)	1.1x10 ⁻⁰¹	0.98 (0.95-1.02)	3.9x10 ⁻⁰¹	1.00 (0.96-1.03)	7.8x10 ⁻⁰¹	1.8x10 ⁻⁰¹	0.99 (0.96-1.03)
1q21.2	rs12048493	[3]	1	149927034	A/C	0.38	1.03 (0.96-1.11)	3.5x10 ⁻⁰¹	1.02 (0.98-1.07)	2.5x10 ⁻⁰¹	1.05 (1.02-1.09)	2.3x10 ⁻⁰³	1.3x10 ⁻⁰³	1.03 (1.00-1.07)
1q32.1	rs4951011	[4]	1	203766331	A/G	0.16	1.03 (0.96-1.11)	4.0x10 ⁻⁰¹	1.03 (0.98-1.09)	2.8x10 ⁻⁰¹	1.07 (1.02-1.11)	2.8x10 ⁻⁰³	1.9x10 ⁻⁰³	1.04 (0.99-1.09)
1q43	rs72755295	[3]	1	242034263	A/G	0.03	0.93 (0.70-1.23)	6.1x10 ⁻⁰¹	1.20 (1.08-1.33)	4.4x10 ⁻⁰⁴	1.09 (1.00-1.19)	5.6x10 ⁻⁰²	3.9x10 ⁻⁰⁴	1.13 (1.02-1.25)
2q14.1	rs4849887	[1]	2	121245122	C/T	0.10	0.98 (0.90-1.07)	6.7x10 ⁻⁰¹	0.90 (0.85-0.96)	2.2x10 ⁻⁰³	0.85 (0.81-0.90)	1.7x10 ⁻⁰⁸	4.1x10 ⁻⁰⁹	0.99 (0.93-1.05)
2q31.1	rs2016394	[1]	2	172972971	G/A	0.47	1.06 (1.00-1.11)	3.9x10 ⁻⁰²	1.00 (0.96-1.03)	8.2x10 ⁻⁰¹	1.00 (0.97-1.03)	9.8x10 ⁻⁰¹	4.5x10 ⁻⁰¹	1.03 (0.99-1.07)
2q31.1	rs1550623	[1]	2	174212894	A/G	0.15	0.99 (0.92-1.06)	7.6x10 ⁻⁰¹	0.95 (0.91-1.01)	7.8x10 ⁻⁰²	1.00 (0.95-1.04)	8.5x10 ⁻⁰¹	2.0x10 ⁻⁰¹	0.99 (0.94-1.04)
2q33.1	rs1830298	[5],[6]	2	202181247	T/C	0.28	1.09 (1.03-1.16)	3.3x10 ⁻⁰³	1.03 (0.99-1.07)	1.5x10 ⁻⁰¹	1.08 (1.04-1.12)	3.0x10 ⁻⁰⁵	7.4x10 ⁻⁰⁷	1.08 (1.04-1.13)
2q35	rs34005590	[7]	2	217963060	C/A	0.05	0.86 (0.72-1.02)	7.9x10 ⁻⁰²	0.93 (0.85-1.02)	1.3x10 ⁻⁰¹	0.98 (0.91-1.05)	5.4x10 ⁻⁰¹	5.5x10 ⁻⁰²	0.99 (0.91-1.08)
2q35	rs4442975	[8],[9]	2	217920769	G/T	0.50	0.96 (0.91-1.01)	8.9x10 ⁻⁰²	0.95 (0.92-0.99)	9.6x10 ⁻⁰³	0.94 (0.92-0.98)	4.9x10 ⁻⁰⁴	3.4x10 ⁻⁰⁶	0.99 (0.96-1.03)
2q35	rs16857609	[1]	2	218296508	C/T	0.26	1.07 (1.01-1.14)	2.6x10 ⁻⁰²	1.09 (1.04-1.13)	1.0x10 ⁻⁰⁴	1.07 (1.03-1.10)	5.2x10 ⁻⁰⁴	1.8x10 ⁻⁰⁸	1.04 (1.00-1.09)
3p26.1	rs6762644	[1]	3	4742276	A/G	0.38	0.97 (0.92-1.03)	3.0x10 ⁻⁰¹	1.02 (0.98-1.06)	2.8x10 ⁻⁰¹	1.04 (1.01-1.08)	1.2x10 ⁻⁰²	5.3x10 ⁻⁰²	1.03 (0.99-1.07)
3p24.1	rs4973768	[10]	3	27416013	C/T	0.47	1.03 (0.98-1.08)	3.0x10 ⁻⁰¹	1.05 (1.01-1.09)	9.0x10 ⁻⁰³	1.04 (1.01-1.07)	1.4x10 ⁻⁰²	2.4x10 ⁻⁰⁴	1.01 (0.98-1.05)
3p.24.1	rs12493607	[1]	3	30682939	G/C	0.34	0.99 (0.93-1.04)	6.1x10 ⁻⁰¹	1.02 (0.98-1.06)	3.7x10 ⁻⁰¹	1.00 (0.96-1.03)	7.9x10 ⁻⁰¹	9.0x10 ⁻⁰¹	1.00 (0.96-1.04)
3p21.31	rs6796502	[3]	3	46866866	G/A	0.10	0.96 (0.87-1.05)	3.3x10 ⁻⁰¹	0.95 (0.89-1.01)	1.0x10 ⁻⁰¹	0.92 (0.87-0.97)	2.7x10 ⁻⁰³	6.5x10 ⁻⁰⁴	0.99 (0.94-1.05)
3p14.1	rs1053338	[11]	3	63967900	A/G	0.14	1.01 (0.93-1.09)	8.3x10 ⁻⁰¹	1.06 (1.00-1.12)	3.7x10 ⁻⁰²	1.03 (0.99-1.08)	1.8x10 ⁻⁰¹	2.5x10 ⁻⁰²	1.00 (0.95-1.05)
4q24	rs9790517	[1]	4	106084778	C/T	0.23	1.09 (1.02-1.16)	8.3x10 ⁻⁰³	1.03 (0.98-1.07)	2.8x10 ⁻⁰¹	0.98 (0.94-1.02)	2.3x10 ⁻⁰¹	3.5x10 ⁻⁰¹	1.01 (0.96-1.05)
4q34.1	rs6828523	[1]	4	175846426	C/A	0.12	0.94 (0.87-1.02)	1.6x10 ⁻⁰¹	1.02 (0.96-1.08)	4.8x10 ⁻⁰¹	1.00 (0.95-1.05)	9.3x10 ⁻⁰¹	9.3x10 ⁻⁰¹	1.04 (0.98-1.10)
5p15.33	rs3215401	[12]	5	1296255	A/AG	0.31	0.89 (0.81-0.98)	1.7x10 ⁻⁰²	0.89 (0.85-0.92)	8.4x10 ⁻⁰⁹	0.88 (0.85-0.91)	2.3x10 ⁻¹²	6.4x10 ⁻²¹	0.90 (0.87-0.94)
5p15.1	rs13162653	[3]	5	16187528	G/T	0.45	0.94 (0.89-1.00)	3.9x10 ⁻⁰²	0.96 (0.93-1.00)	6.8x10 ⁻⁰²	0.98 (0.95-1.01)	2.1x10 ⁻⁰¹	5.5x10 ⁻⁰³	0.99 (0.96-1.03)
5p13.3	rs2012709	[3]	5	32567732	C/T	0.48	1.00 (0.95-1.06)	9.2x10 ⁻⁰¹	1.03 (0.99-1.07)	9.8x10 ⁻⁰²	0.98 (0.95-1.01)	1.5x10 ⁻⁰¹	9.9x10 ⁻⁰¹	1.00 (0.96-1.03)
5p12	rs10941679	[13]	5	44706498	A/G	0.25	1.04 (0.98-1.11)	1.9x10 ⁻⁰¹	1.03 (0.99-1.08)	1.5x10 ⁻⁰¹	1.03 (1.00-1.07)	8.5x10 ⁻⁰²	9.4x10 ⁻⁰³	1.01 (0.96-1.05)
5q11.2	rs62355902	[14],[15]	5	56053723	A/T	0.16	1.06 (0.99-1.14)	1.0x10 ⁻⁰¹	1.10 (1.05-1.15)	2.3x10 ⁻⁰⁴	1.06 (1.02-1.11)	6.7x10 ⁻⁰³	2.1x10 ⁻⁰⁶	1.02 (0.97-1.07)
5q11.2	rs10472076	[1]	5	58184061	T/C	0.38	1.04 (0.99-1.10)	1.3x10 ⁻⁰¹	1.06 (1.02-1.10)	4.6x10 ⁻⁰³	1.03 (1.00-1.07)	4.0x10 ⁻⁰²	2.0x10 ⁻⁰⁴	1.02 (0.98-1.05)
5q11.2	rs1353747	[1]	5	58337481	T/G	0.09	0.97 (0.88-1.06)	4.8x10 ⁻⁰¹	0.92 (0.86-0.98)	8.4x10 ⁻⁰³	0.98 (0.92-1.03)	3.8x10 ⁻⁰¹	1.5x10 ⁻⁰²	0.97 (0.91-1.04)
5q14.2	rs7707921	[3]	5	81538046	A/T	0.25	0.97 (0.91-1.03)	3.0x10 ⁻⁰¹	0.97 (0.93-1.02)	2.0x10 ⁻⁰¹	0.97 (0.93-1.00)	7.6x10 ⁻⁰²	1.5x10 ⁻⁰²	1.02 (0.98-1.07)
5q14.3	rs10474352	[4]	5	90732225	C/T	0.16	0.96 (0.90-1.04)	3.4x10 ⁻⁰¹	1.00 (0.94-1.06)	9.8x10 ⁻⁰¹	0.98 (0.94-1.03)	4.1x10 ⁻⁰¹	3.1x10 ⁻⁰¹	0.99 (0.94-1.04)
5q33.3	rs1432679	[1]	5	158244083	T/C	0.43	1.05 (1.00-1.11)	6.3x10 ⁻⁰²	1.08 (1.04-1.13)	2.4x10 ⁻⁰⁵	1.08 (1.04-1.11)	4.0x10 ⁻⁰⁶	1.1x10 ⁻¹⁰	1.04 (1.01-1.08)
6p25.3	rs11242675	[1]	6	1318878	T/C	0.37	0.93 (0.88-0.98)	6.8x10 ⁻⁰³	0.96 (0.92-0.99)	2.2x10 ⁻⁰²	0.99 (0.96-1.02)	5.1x10 ⁻⁰¹	3.3x10 ⁻⁰³	0.96 (0.93-1.00)
6p24.3	rs9348512	[16]	6	10456706	C/A	0.33	1.02 (0.96-1.08)	5.3x10 ⁻⁰¹	0.99 (0.95-1.03)	6.7x10 ⁻⁰¹	1.01 (0.98-1.05)	5.1x10 ⁻⁰¹	6.5x10 ⁻⁰¹	1.01 (0.97-1.05)
6p23	rs204247	[1]	6	13722523	A/G	0.44	1.08 (1.03-1.14)	3.5x10 ⁻⁰³	1.01 (0.97-1.04)	7.4x10 ⁻⁰¹	1.00 (0.97-1.03)	9.9x10 ⁻⁰¹	1.6x10 ⁻⁰¹	1.01 (0.97-1.05)
6p22.1	rs9257408	[3]	6	28926220	G/C	0.41	1.07 (1.01-1.13)	2.0x10 ⁻⁰²	1.05 (1.01-1.09)	1.4x10 ⁻⁰²	1.03 (1.00-1.07)	5.9x10 ⁻⁰²	2.0x10 ⁻⁰⁴	1.03 (1.00-1.07)
6q14.1	rs17529111	[17]	6	81218386	T/C	0.22	1.12 (1.05-1.19)	5.3x10 ⁻⁰⁴	1.05 (1.00-1.09)	4.7x10 ⁻⁰²	1.06 (1.02-1.10)	1.5x10 ⁻⁰³	1.6x10 ⁻⁰⁶	1.01 (0.96-1.05)
6q25.1	rs9485372	[18]	6	149608874	G/A	0.19	1.02 (0.95-1.09)	5.9x10 ⁻⁰¹	0.95 (0.91-1.00)	6.4x10 ⁻⁰²	0.99 (0.95-1.03)	5.1x10 ⁻⁰¹	1.9x10 ⁻⁰¹	1.00 (0.95-1.04)
6q25	rs9397347	[19],[20]	6	151952332	G/A	0.07	1.35 (1.22-1.49)	7.4x10 ⁻⁰⁹	1.29 (1.20-1.38)	6.5x10 ⁻¹³	1.32 (1.25-1.40)	8.3x10 ⁻²²	2.8x10 ⁻⁴⁰	1.20 (1.12-1.28)
7q21.2	rs6964587	[11]	7	91630620	G/T	0.39	1.02 (0.96-1.07)	5.5x10 ⁻⁰¹	1.04 (1.00-1.08)	6.0x10 ⁻⁰²	1.02 (0.98-1.05)	3.3x10 ⁻⁰¹	4.5x10 ⁻⁰²	1.00 (0.97-1.04)
7q32.3	rs4593472	[3]	7	130667121	C/T	0.35	0.93 (0.87-0.98)	1.1x10 ⁻⁰²	0.99 (0.95-1.03)	6.8x10 ⁻⁰¹	0.97 (0.93-1.00)	5.3x10 ⁻⁰²	9.2x10 ⁻⁰³	0.98 (0.94-1.02)
7q34	rs11977670	[31]	7	139942304	G/A	0.43	1.03 (0.97-1.19)	3.4x10 ⁻⁰¹	0.98 (0.95-1.03)	5.9x10 ⁻⁰¹	1.02 (0.99-1.05)	5.5x10 ⁻⁰¹	2.1x10 ⁻⁰¹	1.06 (1.02-1.10)
7q35	rs720475	[1]	7	144074929	G/A	0.25	1.04 (0.97-1.11)	2.8x10 ⁻⁰¹	0.99 (0.95-1.03)	6.9x10 ⁻⁰¹	1.00 (0.96-1.03)	8.0x10 ⁻⁰¹	9.8x10 ⁻⁰¹	0.98 (0.94-1.02)
8p12	rs9693444	[1]	8	29509616	C/A	0.32	1.02 (0.96-1.08)	5.4x10 ⁻⁰¹	1.09 (1.04-1.13)	4.7x10 ⁻⁰⁵	1.02 (0.98-1.05)	2.9x10 ⁻⁰¹	6.4x10 ⁻⁰⁴	1.00 (0.96-1.04)
8p11.23	rs13365225	[3]	8	36858483	A/G	0.18	0.89 (0.83-0.96)	1.7x10 ⁻⁰³	0.93 (0.88-0.98)	3.5x10 ⁻⁰³	0.90 (0.86-0.94)	1.1x10 ⁻⁰⁶	1.4x10 ⁻¹⁰	0.95 (0.91-1.00)
8q21.11	rs6472903	[1]	8	76230301	T/G	0.17	0.98 (0.91-1.05)	5.8x10 ⁻⁰¹	0.94 (0.89-0.99)	1.3x10 ⁻⁰²	0.96 (0.92-1.00)	8.2x10 ⁻⁰²	3.7x10 ⁻⁰³	0.99 (0.95-1.04)
8q21.11	rs2943559	[1]	8	76417937	A									

22q13.1	chr22:39359355	[30]	22	39359355	I/D ⁵	0.04	1.01 (0.90-1.13)	9.2x10 ⁰¹	1.12 (1.05-1.21)	1.3x10 ⁰³	1.09 (1.04-1.14)	8.3x10 ⁰⁴	1.5x10 ⁰⁵	1.01 (0.94-1.08)
22q13.1	rs6001930	[1]	22	40876234	T/C	0.10	1.15 (1.06-1.25)	1.3x10 ⁰³	1.10 (1.04-1.17)	8.7x10 ⁰⁴	1.14 (1.08-1.19)	6.8x10 ⁰⁷	1.6x10 ⁻¹¹	1.06 (1.00-1.13)

*results for ER-negative disease also reported in Michailidou, K. et al. Identification of more than 70 new breast cancer susceptibility loci for breast cancer and definition of risk-associated genomic features. Reference 1 in the main text
Chr, chromosome; MAF, minor allele frequency; BCAC, Breast Cancer Association Consortium; CIMBA, Consortium of Investigators of Modifiers of BRCA1/2; ⁵More common allele listed first, minor allele second; ⁶31kb deletion
BCAC results were based on GWAS data for 4,480 cases and 12,632 controls, ICOGS data for 7,333 cases and 42,468 controls and OncoArray data 9,655 cases and 45,494 controls
CIMBA results were based on data for 18,908 BRCA1 mutation carriers (9,414 with breast cancer)

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Associations observed with ER-negative breast cancer based on P<0.05 in meta-analysis of all BCAC data
Associations observed with breast cancer for BRCA1 mutation carriers based on P<0.05 in meta-analysis of all CIMBA data

Supplementary Table 11: Associations of 179 breast cancer susceptibility loci with risk for *BRCA2* mutation carriers

How identified	Location	SNP	Alleles [†]	MAF	HR (95%CI)	P-value
Other previous hit for breast cancer	1p36.22	rs616488	A/G	0.32	0.95 (0.91-1.00)	6.3x10 ⁻²
New hit for overall breast cancer	1p36.13	rs2992756	C/T	0.50	1.00 (0.96-1.05)	9.2x10 ⁻¹
New hit for overall breast cancer	1p34.2	rs4233486	T/C	0.36	0.95 (0.90-1.00)	3.6x10 ⁻²
New hit for overall breast cancer	1p34.2	rs79724016	T/G	0.04	0.93 (0.82-1.06)	3.0x10 ⁻¹
New hit for overall breast cancer	1p34.1	rs1707302	G/A	0.32	1.03 (0.98-1.09)	1.9x10 ⁻¹
New hit for overall breast cancer	1p32.3	rs140850326	I/D [†]	0.46	0.99 (0.94-1.03)	5.5x10 ⁻¹
New hit for overall breast cancer	1p22.3	rs17426269	G/A	0.16	1.01 (0.94-1.07)	8.2x10 ⁻¹
Other previous hit for breast cancer	1p13.2	rs11552449	C/T	0.17	1.04 (0.98-1.11)	2.1x10 ⁻¹
New hit for overall breast cancer	1p12	rs7529522	T/C	0.24	1.01 (0.96-1.07)	6.0x10 ⁻¹
Other previous hit for breast cancer	1p11.2	rs11249433	A/G	0.41	1.04 (0.99-1.09)	9.6x10 ⁻²
Other previous hit for breast cancer	1q21.1	rs12405132	C/T	0.35	1.02 (0.97-1.07)	4.9x10 ⁻¹
Other previous hit for breast cancer	1q21.2	rs12048493	A/C	0.38	1.00 (0.95-1.05)	8.6x10 ⁻¹
New hit for overall breast cancer	1q22	rs4971059	G/A	0.34	1.01 (0.96-1.06)	7.5x10 ⁻¹
New hit for overall breast cancer	1q32.1	rs35383942	C/T	0.06	1.13 (1.02-1.25)	1.7x10 ⁻²
Previous hit for ER-negative disease	1q32.1	rs6678914	G/A	0.41	0.99 (0.94-1.04)	5.8x10 ⁻¹
Other previous hit for breast cancer	1q32.1	rs4951011	A/G	0.16	1.02 (0.95-1.08)	6.5x10 ⁻¹
Previous hit for ER-negative disease	1q32.1	rs4245739	A/C	0.28	0.96 (0.91-1.01)	1.2x10 ⁻¹
New hit for overall breast cancer	1q41	rs11117758	G/A	0.22	0.94 (0.89-1.00)	3.7x10 ⁻²
Other previous hit for breast cancer	1q43	rs72755295	A/G	0.03	1.17 (1.02-1.34)	2.5x10 ⁻²
New hit for overall breast cancer	2p25.1	rs113577745	C/G	0.10	1.01 (0.93-1.09)	8.7x10 ⁻¹
Previous hit for ER-negative disease	2p24.1	rs12710696	C/T	0.38	1.00 (0.95-1.05)	9.3x10 ⁻¹
New hit for ER-negative breast cancer	2p23.3	rs200648189	CT/C	0.19	1.00 (0.94-1.07)	9.2x10 ⁻¹
Previous hit for ER-negative disease	2p23.2	rs4577244†	C/T	0.22	0.99 (0.93-1.04)	6.2x10 ⁻¹
New hit for overall breast cancer	2q13	rs71801447	CTTATGTT/C	0.07	1.09 (0.99-1.20)	6.8x10 ⁻²
Other previous hit for breast cancer	2q14.1	rs4849887	C/T	0.11	1.00 (0.93-1.08)	9.9x10 ⁻¹
Other previous hit for breast cancer	2q31.1	rs2016394	G/A	0.46	0.99 (0.94-1.04)	6.0x10 ⁻¹
Other previous hit for breast cancer	2q31.1	rs1550623	A/G	0.15	1.00 (0.94-1.07)	9.7x10 ⁻¹
Other previous hit for breast cancer	2q33.1	rs1830298	T/C	0.30	1.02 (0.97-1.07)	4.9x10 ⁻¹
Other previous hit for breast cancer	2q35	rs4442975	G/T	0.49	0.98 (0.94-1.03)	4.7x10 ⁻¹
Other previous hit for breast cancer	2q35	rs34005590	C/A	0.04	0.98 (0.88-1.11)	7.9x10 ⁻¹
Other previous hit for breast cancer	2q35	rs16857609	C/T	0.27	0.97 (0.92-1.02)	1.9x10 ⁻¹
New hit for overall breast cancer	2q36.3	rs12479355	A/G	0.21	0.94 (0.89-1.00)	5.0x10 ⁻²
Other previous hit for breast cancer	3p26.1	rs6762644	A/G	0.37	0.99 (0.94-1.04)	5.9x10 ⁻¹
Other previous hit for breast cancer	3p24.1	rs4973768	C/T	0.50	1.07 (1.02-1.12)	4.1x10 ⁻³
Other previous hit for breast cancer	3p.24.1	rs12493607	G/C	0.33	1.01 (0.96-1.06)	7.5x10 ⁻¹
Other previous hit for breast cancer	3p21.31	rs6796502	G/A	0.10	1.03 (0.95-1.11)	4.8x10 ⁻¹
Other previous hit for breast cancer	3p14.1	rs1053338	A/G	0.14	1.02 (0.96-1.09)	4.9x10 ⁻¹
New hit for overall breast cancer	3p13	rs6805189	T/C	0.47	1.03 (0.98-1.08)	2.1x10 ⁻¹
New hit for overall breast cancer	3p12.1	rs13066793	A/G	0.09	0.91 (0.84-0.99)	3.6x10 ⁻²
New hit for overall breast cancer	3p12.1	rs9833888	G/T	0.22	1.04 (0.98-1.10)	2.2x10 ⁻¹
New hit for overall breast cancer	3q23	rs34207738	CTT/C	0.40	0.98 (0.94-1.03)	4.4x10 ⁻¹
New hit for overall breast cancer	3q26.31	rs58058861	G/A	0.21	1.03 (0.97-1.09)	3.5x10 ⁻¹
New hit for overall breast cancer	4p14	rs6815814	A/C	0.28	0.96 (0.91-1.01)	1.3x10 ⁻¹
New hit for overall breast cancer	4q21.23	4:84370124	TA/TAA	0.49	0.98 (0.94-1.03)	4.8x10 ⁻¹
New hit for overall breast cancer	4q22.1	rs10022462	C/T	0.45	0.99 (0.94-1.04)	6.3x10 ⁻¹
Other previous hit for breast cancer	4q24	rs9790517	C/T	0.22	0.98 (0.93-1.04)	5.4x10 ⁻¹
New hit for overall breast cancer	4q28.1	rs77528541	G/T	0.12	0.94 (0.87-1.02)	1.3x10 ⁻¹
Other previous hit for breast cancer	4q34.1	rs6828523	C/A	0.11	0.97 (0.90-1.04)	4.0x10 ⁻¹
New hit for overall breast cancer	5p15.33	rs116095464	T/C	0.06	1.04 (0.93-1.15)	5.0x10 ⁻¹
Previous hit for ER-negative disease	5p15.33	rs10069690	C/T	0.27	1.06 (1.01-1.12)	2.7x10 ⁻²
Other previous hit for breast cancer	5p15.33	rs3215401	A/AG	0.31	0.94 (0.89-0.98)	1.0x10 ⁻²
Other previous hit for breast cancer	5p15.1	rs13162653	G/T	0.44	1.05 (1.00-1.10)	6.4x10 ⁻²
Other previous hit for breast cancer	5p13.3	rs2012709	C/T	0.49	1.01 (0.96-1.05)	8.0x10 ⁻¹
Other previous hit for breast cancer	5p12	rs10941679	A/G	0.24	1.09 (1.03-1.15)	1.9x10 ⁻³
New hit for overall breast cancer	5q11.1	rs72749841	T/C	0.16	0.98 (0.91-1.06)	6.5x10 ⁻¹
New hit for overall breast cancer	5q11.1	rs35951924	A/AT	0.32	0.96 (0.91-1.02)	1.9x10 ⁻¹
Other previous hit for breast cancer	5q11.2	rs62355902	A/T	0.16	1.10 (1.03-1.17)	4.0x10 ⁻³
Other previous hit for breast cancer	5q11.2	rs10472076	T/C	0.38	1.02 (0.97-1.07)	4.9x10 ⁻¹
Other previous hit for breast cancer	5q11.2	rs1353747	T/G	0.09	0.94 (0.86-1.01)	1.0x10 ⁻¹
Other previous hit for breast cancer	5q14.2	rs7707921	A/T	0.25	1.00 (0.95-1.05)	9.4x10 ⁻¹
Other previous hit for breast cancer	5q14.3	rs10474352	C/T	0.15	0.98 (0.91-1.04)	4.6x10 ⁻¹

New hit for overall breast cancer	5q22.1	rs6882649	T/G	0.32	0.97 (0.92-1.02)	2.5x10 ⁻¹
New hit for overall breast cancer	5q31.1	rs6596100	C/T	0.23	0.97 (0.91-1.02)	2.4x10 ⁻¹
Other previous hit for breast cancer	5q33.3	rs1432679	T/C	0.45	1.03 (0.98-1.08)	2.0x10 ⁻¹
New hit for overall breast cancer	5q35.1	rs4562056	G/T	0.36	1.01 (0.96-1.06)	7.4x10 ⁻¹
Other previous hit for breast cancer	6p25.3	rs11242675	T/C	0.35	1.01 (0.96-1.06)	7.4x10 ⁻¹
Other previous hit for breast cancer	6p24.3	rs9348512	C/A	0.34	0.87 (0.83-0.91)	1.9x10 ⁻⁸
Other previous hit for breast cancer	6p23	rs204247	A/G	0.45	1.08 (1.03-1.13)	1.1x10 ⁻³
New hit for overall breast cancer	6p22.3	rs3819405	C/T	0.34	0.97 (0.92-1.02)	2.0x10 ⁻¹
New hit for overall breast cancer	6p22.3	rs2223621	C/T	0.37	1.03 (0.98-1.08)	2.8x10 ⁻¹
New hit for overall breast cancer	6p22.2	rs71557345	G/A	0.07	1.02 (0.93-1.13)	6.5x10 ⁻¹
Other previous hit for breast cancer	6p22.1	rs9257408	G/C	0.43	1.00 (0.95-1.05)	9.9x10 ⁻¹
New hit for overall breast cancer	6q14.1	rs12207986	A/G	0.46	0.97 (0.93-1.02)	2.3x10 ⁻¹
Other previous hit for breast cancer	6q14.1	rs17529111	T/C	0.22	1.06 (1.00-1.12)	3.9x10 ⁻²
New hit for ER-negative breast cancer	6q23.1	rs6569648	T/C	0.23	0.97 (0.92-1.02)	2.6x10 ⁻¹
Other previous hit for breast cancer	6q25.1	rs9485372	G/A	0.19	0.92 (0.87-0.98)	8.0x10 ⁻³
Previous hit for ER-negative disease	6q25.1	rs3757322†	T/G	0.35	1.07 (1.02-1.12)	5.9x10 ⁻³
Other previous hit for breast cancer	6q25	rs9397437	G/A	0.08	1.12 (1.03-1.22)	8.6x10 ⁻³
Previous hit for ER-negative disease	6q25.2	rs2747652†	C/T	0.48	0.98 (0.93-1.02)	3.3x10 ⁻¹
New hit for overall breast cancer	7p15.3	rs7971	A/G	0.35	0.96 (0.91-1.01)	9.4x10 ⁻²
New hit for overall breast cancer	7p15.1	rs17156577	T/C	0.12	1.03 (0.95-1.10)	4.9x10 ⁻¹
Other previous hit for breast cancer	7q21.2	rs6964587	G/T	0.41	1.05 (1.00-1.10)	6.9x10 ⁻²
New hit for overall breast cancer	7q21.3	rs17268829	T/C	0.28	1.00 (0.95-1.05)	8.8x10 ⁻¹
New hit for overall breast cancer	7q22.1	rs71559437	G/A	0.12	1.09 (1.01-1.18)	2.0x10 ⁻²
Other previous hit for breast cancer	7q32.3	rs4593472	C/T	0.33	1.03 (0.98-1.08)	2.8x10 ⁻¹
Other previous hit for breast cancer	7q34	rs11977670	G/A	0.44	1.02 (0.98-1.07)	3.5x10 ⁻¹
Other previous hit for breast cancer	7q35	rs720475	G/A	0.26	0.99 (0.94-1.04)	6.2x10 ⁻¹
New hit for ER-negative breast cancer	8p23.3	rs66823261	T/C	0.22	1.02 (0.96-1.08)	5.5x10 ⁻¹
Other previous hit for breast cancer	8p12	rs9693444	C/A	0.33	0.99 (0.94-1.04)	6.0x10 ⁻¹
Other previous hit for breast cancer	8p11.23	rs13365225	A/G	0.18	0.98 (0.92-1.04)	4.6x10 ⁻¹
Other previous hit for breast cancer	8q21.11	rs6472903	T/G	0.17	0.95 (0.89-1.02)	1.3x10 ⁻¹
Other previous hit for breast cancer	8q21.11	rs2943559	A/G	0.09	1.08 (0.99-1.17)	7.0x10 ⁻²
New hit for overall breast cancer	8q22.3	rs514192	T/A	0.33	1.01 (0.96-1.06)	6.4x10 ⁻¹
New hit for overall breast cancer	8q23.1	rs12546444	A/T	0.10	0.97 (0.90-1.05)	4.8x10 ⁻¹
Other previous hit for breast cancer	8q23.3	rs13267382	G/A	0.35	1.00 (0.96-1.05)	8.6x10 ⁻¹
New hit for ER-negative breast cancer	8q24.13	rs17350191	C/T	0.35	1.00 (0.95-1.05)	9.2x10 ⁻¹
Other previous hit for breast cancer	8q24.21	rs13281615	A/G	0.42	1.05 (1.00-1.10)	6.1x10 ⁻²
Other previous hit for breast cancer	8q24.21	rs11780156	C/T	0.19	0.99 (0.93-1.05)	7.7x10 ⁻¹
Other previous hit for breast cancer	9p21.3	rs1011970	G/T	0.17	1.04 (0.98-1.11)	2.1x10 ⁻¹
Other previous hit for breast cancer	9q31.2	rs10759243	C/A	0.29	1.05 (1.00-1.10)	7.6x10 ⁻²
Other previous hit for breast cancer	9q31.2	rs10816625	A/G	0.07	0.96 (0.88-1.06)	4.3x10 ⁻¹
Other previous hit for breast cancer	9q31.2	rs13294895	C/T	0.17	1.04 (0.98-1.11)	1.8x10 ⁻¹
Other previous hit for breast cancer	9q31.2	rs676256	T/C	0.36	1.00 (0.95-1.05)	9.3x10 ⁻¹
New hit for overall breast cancer	9q33.1	rs1895062	A/G	0.40	1.00 (0.95-1.05)	9.9x10 ⁻¹
New hit for overall breast cancer	9q33.3	rs10760444	A/G	0.44	0.98 (0.94-1.03)	4.9x10 ⁻¹
New hit for overall breast cancer	9q34.2	rs587745765	I/D†	0.21	1.01 (0.95-1.07)	8.1x10 ⁻¹
Other previous hit for breast cancer	10p15.1	rs2380205	C/T	0.43	0.99 (0.95-1.04)	7.1x10 ⁻¹
New hit for overall breast cancer	10p14	rs67958007	TG/T	0.13	1.10 (1.03-1.18)	6.6x10 ⁻³
Other previous hit for breast cancer	10p12.31	rs7072776	G/A	0.30	1.03 (0.98-1.08)	2.8x10 ⁻¹
Other previous hit for breast cancer	10p12.31	rs11814448	A/C	0.02	1.03 (0.88-1.21)	6.8x10 ⁻¹
Other previous hit for breast cancer	10q21.2	rs10995201	A/G	0.15	0.95 (0.89-1.01)	1.0x10 ⁻¹
Other previous hit for breast cancer	10q22.3	rs704010	C/T	0.38	1.02 (0.98-1.07)	3.3x10 ⁻¹
New hit for overall breast cancer	10q23.33	rs140936696	C/CAA	0.17	1.01 (0.94-1.07)	8.3x10 ⁻¹
Other previous hit for breast cancer	10q25.2	rs7904519	A/G	0.47	1.01 (0.96-1.06)	6.5x10 ⁻¹
Other previous hit for breast cancer	10q26.12	rs11199914	C/T	0.33	0.94 (0.89-0.98)	9.3x10 ⁻³
Other previous hit for breast cancer	10q26.13	rs2981578	T/C	0.51	1.20 (1.14-1.25)	1.1x10 ⁻¹³
Other previous hit for breast cancer	10q26.13	rs35054928	G/GC	0.44	1.23 (1.17-1.29)	5.8x10 ⁻¹⁸
Other previous hit for breast cancer	10q26.13	rs45631563	A/T	0.05	0.84 (0.75-0.94)	1.9x10 ⁻³
New hit for overall breast cancer	11p15	rs6597981	G/A	0.50	0.96 (0.92-1.01)	1.3x10 ⁻¹
Other previous hit for breast cancer	11p15.5	rs3817198	T/C	0.33	1.10 (1.04-1.15)	2.8x10 ⁻⁴
Other previous hit for breast cancer	11q13.1	rs3903072	G/T	0.47	0.97 (0.92-1.02)	2.0x10 ⁻¹
Other previous hit for breast cancer	11q13.3	rs554219	C/G	0.13	1.07 (1.00-1.15)	4.4x10 ⁻²
Other previous hit for breast cancer	11q13.3	rs75915166	C/A	0.06	1.04 (0.94-1.15)	4.1x10 ⁻¹
New hit for ER-negative breast cancer	11q22.3	rs11374964	G/GA	0.43	1.02 (0.97-1.07)	3.8x10 ⁻¹

New hit for ER-negative breast cancer	11q22.3	rs74911261	G/A	0.02	0.94 (0.80-1.09)	4.2x10 ⁻¹
Other previous hit for breast cancer	11q24.3	rs11820646	C/T	0.39	0.92 (0.88-0.97)	1.2x10 ⁻³
Other previous hit for breast cancer	12p13.1	rs12422552	G/C	0.28	0.99 (0.94-1.04)	7.3x10 ⁻¹
Other previous hit for breast cancer	12p11.22	rs7297051	C/T	0.23	0.92 (0.87-0.97)	2.5x10 ⁻³
New hit for overall breast cancer	12q21.31	12:85009437:T:C	T/C	0.32	1.04 (0.98-1.09)	2.0x10 ⁻¹
Other previous hit for breast cancer	12q22	rs17356907	A/G	0.30	1.01 (0.96-1.07)	6.0x10 ⁻¹
Other previous hit for breast cancer	12q24.21	rs1292011	A/G	0.41	0.95 (0.90-0.99)	3.0x10 ⁻²
New hit for overall breast cancer	12q24.31	12:120832146:C:T	C/T	0.15	1.02 (0.95-1.09)	6.0x10 ⁻¹
Other previous hit for breast cancer	13q13.1	rs11571833	A/T	0.03	0.99 (0.85-1.14)	8.4x10 ⁻¹
Previous hit for ER-negative disease	13q22.1	rs6562760†	G/A	0.25	0.96 (0.91-1.01)	1.1x10 ⁻¹
Other previous hit for breast cancer	14q13.3	rs2236007	G/A	0.21	0.97 (0.92-1.03)	3.9x10 ⁻¹
Other previous hit for breast cancer	14q24.1	rs2588809	C/T	0.20	1.05 (0.99-1.11)	1.1x10 ⁻¹
Other previous hit for breast cancer	14q24.1	rs999737	C/T	0.22	0.95 (0.90-1.00)	6.9x10 ⁻²
Other previous hit for breast cancer	14q32.11	rs941764	A/G	0.34	1.02 (0.97-1.07)	5.1x10 ⁻¹
Other previous hit for breast cancer	14q32.12	rs11627032	T/C	0.26	1.01 (0.96-1.07)	7.5x10 ⁻¹
New hit for overall breast cancer	14q32.33	rs10623258	C/CTT	0.46	1.00 (0.95-1.05)	9.2x10 ⁻¹
Other previous hit for breast cancer	15q26.1	rs2290203	G/A	0.21	0.95 (0.90-1.01)	1.1x10 ⁻¹
New hit for ER-negative breast cancer	16p13.3	rs11076805	C/A	0.26	0.93 (0.88-0.99)	1.3x10 ⁻²
Other previous hit for breast cancer	16q12.1	rs4784227	C/T	0.27	1.21 (1.15-1.28)	6.8x10 ⁻¹³
Other previous hit for breast cancer	16q12.2	rs17817449	T/G	0.40	0.97 (0.93-1.02)	2.5x10 ⁻¹
Previous hit for ER-negative disease	16q12.2	rs11075995	T/A	0.23	1.03 (0.98-1.09)	2.6x10 ⁻¹
New hit for overall breast cancer	16q12.2	rs28539243	G/A	0.49	1.01 (0.96-1.06)	6.4x10 ⁻¹
New hit for overall breast cancer	16q13	rs2432539	G/A	0.40	1.04 (0.99-1.09)	1.1x10 ⁻¹
Other previous hit for breast cancer	16q23.2	rs13329835	A/G	0.24	1.05 (0.99-1.10)	1.2x10 ⁻¹
New hit for overall breast cancer	16q24.2	rs4496150	C/A	0.26	0.97 (0.92-1.02)	2.9x10 ⁻¹
Other previous hit for breast cancer	17q11.2	chr17:29230520	GGT/G	0.27	0.92 (0.87-0.97)	2.4x10 ⁻³
New hit for overall breast cancer	17q21.2	rs72826962	C/T	0.01	1.21 (0.98-1.50)	7.3x10 ⁻²
New hit for overall breast cancer	17q21.31	17:44252468:G:A	G/A	0.20	0.90 (0.85-0.96)	6.1x10 ⁻⁴
Other previous hit for breast cancer	17q22	rs2787486	A/C	0.29	1.02 (0.97-1.07)	5.3x10 ⁻¹
Other previous hit for breast cancer	17q25.3	rs745570	G/A	0.50	1.03 (0.98-1.08)	2.2x10 ⁻¹
Other previous hit for breast cancer	18q11.2	rs527616	G/C	0.37	0.98 (0.93-1.03)	4.2x10 ⁻¹
Other previous hit for breast cancer	18q11.2	rs1436904	T/G	0.39	0.98 (0.93-1.02)	3.3x10 ⁻¹
New hit for ER-negative breast cancer	18q12.1	rs36194942	A/AT	0.31	0.99 (0.94-1.04)	6.2x10 ⁻¹
New hit for overall breast cancer	18q12.1	rs117618124	T/C	0.04	0.93 (0.83-1.06)	2.9x10 ⁻¹
Other previous hit for breast cancer	18q12.3	rs6507583	A/G	0.07	0.9 (0.82-0.99)	2.2x10 ⁻²
New hit for ER-negative breast cancer	19p13.2	rs322144	C/G	0.45	0.98 (0.93-1.03)	4.2x10 ⁻¹
New hit for overall breast cancer	19p13.13	rs78269692	T/C	0.05	0.98 (0.87-1.10)	6.9x10 ⁻¹
New hit for overall breast cancer	19p13.12	rs2594714	G/A	0.22	0.99 (0.93-1.05)	7.3x10 ⁻¹
Previous hit for ER-negative disease	19p13.11	rs67397200	C/G	0.30	1.00 (0.95-1.05)	8.6x10 ⁻¹
Other previous hit for breast cancer	19p13.11	rs4808801	A/G	0.33	0.97 (0.92-1.02)	1.8x10 ⁻¹
New hit for overall breast cancer	19p13.11	rs2965183	G/A	0.36	1.06 (1.01-1.12)	1.6x10 ⁻²
New hit for ER-negative breast cancer	19q12	rs113701136	C/T	0.32	1.06 (1.01-1.12)	1.7x10 ⁻²
Other previous hit for breast cancer	19q13.31	rs3760982	G/A	0.46	1.02 (0.97-1.07)	3.7x10 ⁻¹
New hit for overall breast cancer	19q13.22	rs71338792	A/AT	0.23	1.04 (0.98-1.10)	2.3x10 ⁻¹
New hit for overall breast cancer	20p12.3	rs16991615	G/A	0.07	1.00 (0.92-1.10)	9.3x10 ⁻¹
Previous hit for ER-negative disease	20q11.21	rs2284378	C/T	0.31	1.02 (0.97-1.07)	4.9x10 ⁻¹
New hit for overall breast cancer	20q13.13	rs6122906	A/G	0.19	1.06 (1.00-1.12)	7.0x10 ⁻²
Other previous hit for breast cancer	21q21.1	rs2823093	G/A	0.27	0.94 (0.89-0.99)	1.4x10 ⁻²
Other previous hit for breast cancer	22q12.1	rs17879961	A/G	0.004	1.83 (1.23-2.71)	2.7x10 ⁻³
Other previous hit for breast cancer	22q12.2	rs132390	T/C	0.03	1.09 (0.96-1.24)	1.9x10 ⁻¹
New hit for overall breast cancer	22q13.1	rs738321	C/G	0.38	0.97 (0.92-1.02)	2.1x10 ⁻¹
Other previous hit for breast cancer	22q13.1	chr22:39359355	I/D [§]	0.004	1.67 (0.97-2.88)	6.3x10 ⁻²
Other previous hit for breast cancer	22q13.1	rs6001930	T/C	0.10	1.02 (0.95-1.11)	5.5x10 ⁻¹
New hit for overall breast cancer	22q13.2	rs73161324	C/T	0.05	1.01 (0.91-1.13)	7.8x10 ⁻¹
New hit for overall breast cancer	22q13.31	rs28512361	G/A	0.11	0.98 (0.91-1.06)	6.3x10 ⁻¹

Chr, chromosome; MAF, minor allele frequency; † More common allele listed first, minor allele second;

‡ 21 base-pair deletion; § 36 base-pair deletion; ¶ 14 base-pair insertion; § 31 kb deletion

Results based on OncoArray data for 10,988 *BRCA2* mutation carriers (5,611 with breast cancer) and iCOGS data for 1,418 *BRCA2* mutation carriers (755 with breast cancer), all from the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA)

Supplementary Table 12: Detailed informat

Theme

[illegible]

[illegible]

APOPTOSIS

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APOPTOSIS

APOPTOSIS

CELL AGING/TELOMERE

CELL AGING/TELOMERE

CELL AGING/TELOMERE

CELL AGING/TELOMERE

CELL AGING/TELOMERE

CELL AGING/TELOMERE

CELL AGING/TELOMERE

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CELL CYCLE/DNA DAMAGE RESPONSE

CELL CYCLE/DNA DAMAGE RESPONSE

CELL CYCLE/DNA DAMAGE RESPONSE

CELL CYCLE/DNA DAMAGE RESPONSE

CELL CYCLE/DNA DAMAGE RESPONSE

CELL CYCLE/DNA DAMAGE RESPONSE

[illegible]

[illegible]

OTHER-NOT CLUSTERED

OTHER-NOT CLUSTERED

†Standardized Enrichment Score is the actual val

tion about themes and pathways appearing in the enrichment maps (Supplementary Figur

Pathway

ACTIVATION OF NMDA RECEPTOR UPON GLUTAMATE BINDING AND POSTSYNAPTIC EVENT:
ACTIVATION OF PROTEIN KINASE A ACTIVITY
ACTIVATION OF PROTEIN KINASE A ACTIVITY
ADENYLATE CYCLASE ACTIVATING PATHWAY
ADENYLATE CYCLASE ACTIVATING PATHWAY
ADENYLATE CYCLASE INHIBITORY PATHWAY
ADENYLATE CYCLASE INHIBITORY PATHWAY
ADENYLATE CYCLASE-ACTIVATING ADRENERGIC RECEPTOR SIGNALING PATHWAY
ADENYLATE CYCLASE-ACTIVATING ADRENERGIC RECEPTOR SIGNALING PATHWAY
ADENYLATE CYCLASE-ACTIVATING G-PROTEIN COUPLED RECEPTOR SIGNALING PATHWAY
ADENYLATE CYCLASE-ACTIVATING G-PROTEIN COUPLED RECEPTOR SIGNALING PATHWAY
ADENYLATE CYCLASE-ACTIVATING G-PROTEIN COUPLED RECEPTOR SIGNALING PATHWAY
ADENYLATE CYCLASE-ACTIVATING G-PROTEIN COUPLED RECEPTOR SIGNALING PATHWAY
ADENYLATE CYCLASE-INHIBITING G-PROTEIN COUPLED RECEPTOR SIGNALING PATHWAY
ADENYLATE CYCLASE-INHIBITING G-PROTEIN COUPLED RECEPTOR SIGNALING PATHWAY
ADENYLATE CYCLASE-INHIBITING G-PROTEIN COUPLED RECEPTOR SIGNALING PATHWAY
ADENYLATE CYCLASE-INHIBITING G-PROTEIN COUPLED RECEPTOR SIGNALING PATHWAY
ADRENERGIC RECEPTOR SIGNALING PATHWAY
ADRENERGIC RECEPTOR SIGNALING PATHWAY
CA-DEPENDENT EVENTS
CA-DEPENDENT EVENTS
CALMODULIN INDUCED EVENTS
CALMODULIN INDUCED EVENTS
CAM PATHWAY
CAM PATHWAY
CAMP BIOSYNTHETIC PROCESS
CAMP BIOSYNTHETIC PROCESS
CAMP METABOLIC PROCESS
CAMP METABOLIC PROCESS
CAMP METABOLIC PROCESS
CAMP METABOLIC PROCESS
CAMP-MEDIATED SIGNALING
CAMP-MEDIATED SIGNALING
CAMP-MEDIATED SIGNALING
CYCLIC NUCLEOTIDE METABOLIC PROCESS
CYCLIC NUCLEOTIDE METABOLIC PROCESS
CYCLIC NUCLEOTIDE METABOLIC PROCESS
CYCLIC NUCLEOTIDE METABOLIC PROCESS
CYCLIC-NUCLEOTIDE-MEDIATED SIGNALING
CYCLIC-NUCLEOTIDE-MEDIATED SIGNALING
CYCLIC-NUCLEOTIDE-MEDIATED SIGNALING
DAG AND IP3 SIGNALING
DAG AND IP3 SIGNALING
EGFR INTERACTS WITH PHOSPHOLIPASE C-GAMMA
EGFR INTERACTS WITH PHOSPHOLIPASE C-GAMMA
ENDOTHELIN SIGNALING PATHWAY
ENDOTHELIN SIGNALING PATHWAY

G-PROTEIN MEDIATED EVENTS
G-PROTEIN MEDIATED EVENTS
INHIBITION OF ADENYLATE CYCLASE PATHWAY
INHIBITION OF ADENYLATE CYCLASE PATHWAY
LPA4-MEDIATED SIGNALING EVENTS
LPA4-MEDIATED SIGNALING EVENTS
NEGATIVE REGULATION OF BLOOD CIRCULATION
PHOSPHOLIPASE C-MEDIATED CASCADE: FGFR1
PHOSPHOLIPASE C-MEDIATED CASCADE: FGFR1
PHOSPHOLIPASE C-MEDIATED CASCADE; FGFR2
PHOSPHOLIPASE C-MEDIATED CASCADE; FGFR2
PHOSPHOLIPASE C-MEDIATED CASCADE; FGFR3
PHOSPHOLIPASE C-MEDIATED CASCADE; FGFR3
PHOSPHOLIPASE C-MEDIATED CASCADE; FGFR4
PHOSPHOLIPASE C-MEDIATED CASCADE; FGFR4
PKA ACTIVATION IN GLUCAGON SIGNALLING
PKA ACTIVATION IN GLUCAGON SIGNALLING
PKA ACTIVATION
PKA ACTIVATION
PKA-MEDIATED PHOSPHORYLATION OF CREB
PKA-MEDIATED PHOSPHORYLATION OF CREB
PLC BETA MEDIATED EVENTS
PLC BETA MEDIATED EVENTS
PLC-GAMMA1 SIGNALLING
PLC-GAMMA1 SIGNALLING
PLCG1 EVENTS IN ERBB2 SIGNALING
PLCG1 EVENTS IN ERBB2 SIGNALING
POSITIVE REGULATION OF INTERLEUKIN-2 PRODUCTION
POST NMDA RECEPTOR ACTIVATION EVENTS
PURINE RIBONUCLEOTIDE CATABOLIC PROCESS
PURINE-CONTAINING COMPOUND CATABOLIC PROCESS
PURINE-CONTAINING COMPOUND CATABOLIC PROCESS
REGULATION OF CARDIAC MUSCLE CELL CONTRACTION
REGULATION OF CELL COMMUNICATION BY ELECTRICAL COUPLING
REGULATION OF RELEASE OF SEQUESTERED CALCIUM ION INTO CYTOSOL BY SARCOPLASMI
RIBONUCLEOTIDE CATABOLIC PROCESS
ADHERENS JUNCTION ORGANIZATION
ADHERENS JUNCTIONS INTERACTIONS
ACTIVATION OF CYSTEINE-TYPE ENDOPEPTIDASE ACTIVITY INVOLVED IN APOPTOTIC SIGNAL
ACTIVATION OF CYSTEINE-TYPE ENDOPEPTIDASE ACTIVITY INVOLVED IN APOPTOTIC SIGNAL
APOPTOTIC DNA FRAGMENTATION
BIOCARTA_CASPASE_PATHWAY
BIOCARTA_CASPASE_PATHWAY
BIOCARTA_DEATH_PATHWAY
BIOCARTA_DEATH_PATHWAY
BIOCARTA_DEATH_PATHWAY
BIOCARTA_FAS_PATHWAY
BIOCARTA_FAS_PATHWAY
BIOCARTA_FAS_PATHWAY
BIOCARTA_SODD_PATHWAY
CASP8 ACTIVITY IS INHIBITED

DIMERIZATION OF PROCASPASE-8
IN UTERO EMBRYONIC DEVELOPMENT
MACROPHAGE DIFFERENTIATION
NEGATIVE REGULATION OF EXTRINSIC APOPTOTIC SIGNALING PATHWAY IN ABSENCE OF LIGAND
NEGATIVE REGULATION OF MYOTUBE DIFFERENTIATION
NEGATIVE REGULATION OF SIGNAL TRANSDUCTION IN ABSENCE OF LIGAND
NEGATIVE REGULATION OF STRIATED MUSCLE CELL DIFFERENTIATION
POSITIVE REGULATION OF CYSTEINE-TYPE ENDOPEPTIDASE ACTIVITY INVOLVED IN APOPTOSIS
POSITIVE REGULATION OF CYSTEINE-TYPE ENDOPEPTIDASE ACTIVITY INVOLVED IN APOPTOSIS
REGULATION BY C-FLIP
REGULATION OF EXECUTION PHASE OF APOPTOSIS
REGULATION OF EXECUTION PHASE OF APOPTOSIS
REGULATION OF EXTRINSIC APOPTOTIC SIGNALING PATHWAY IN ABSENCE OF LIGAND
REGULATION OF MACROPHAGE DIFFERENTIATION
SA_CASPASE_CASCADE
SA_CASPASE_CASCADE
TNFR1-INDUCED PROAPOPTOTIC SIGNALING
TRAIL SIGNALING PATHWAY
TRAIL SIGNALING PATHWAY
TRIF-MEDIATED PROGRAMMED CELL DEATH
BIOCARTA_ACH_PATHWAY
BIOCARTA_TEL_PATHWAY
CELL AGING
CELL AGING
CELL AGING
ESTABLISHMENT OF PROTEIN LOCALIZATION TO CHROMOSOME
ESTABLISHMENT OF PROTEIN LOCALIZATION TO CHROMOSOME
EXTENSION OF TELOMERES
HETEROCHROMATIN ORGANIZATION
NEGATIVE REGULATION OF CELL AGING
PROTEIN LOCALIZATION TO CHROMOSOME, TELOMERIC REGION
PROTEIN LOCALIZATION TO CHROMOSOME, TELOMERIC REGION
REGULATION OF CELL AGING
REGULATION OF CELL AGING
REGULATION OF CELLULAR SENESCENCE
REGULATION OF CELLULAR SENESCENCE
REGULATION OF PRI-MIRNA TRANSCRIPTION FROM RNA POLYMERASE II PROMOTER
REPLICATIVE SENESCENCE
REPLICATIVE SENESCENCE
REPLICATIVE SENESCENCE
RNA-DEPENDENT DNA REPLICATION
RNA-DEPENDENT DNA REPLICATION
TELOMERE MAINTENANCE VIA TELOMERASE
TELOMERE MAINTENANCE VIA TELOMERASE
TELOMERE MAINTENANCE
BIOCARTA_G1_PATHWAY
BIOCARTA_G1_PATHWAY
BIOCARTA_G1_PATHWAY
BIOCARTA_P53_PATHWAY
BIOCARTA_P53_PATHWAY
CELL CYCLE

FOXM1 TRANSCRIPTION FACTOR NETWORK
FOXM1 TRANSCRIPTION FACTOR NETWORK
FOXM1 TRANSCRIPTION FACTOR NETWORK
FOXM1 TRANSCRIPTION FACTOR NETWORK
G2 DNA DAMAGE CHECKPOINT
G2 DNA DAMAGE CHECKPOINT
MITOTIC G2/M TRANSITION CHECKPOINT
NEGATIVE REGULATION OF B CELL ACTIVATION
NEGATIVE REGULATION OF B CELL ACTIVATION
NEGATIVE REGULATION OF G2/M TRANSITION OF MITOTIC CELL CYCLE
POSITIVE REGULATION OF CELL CYCLE G2/M PHASE TRANSITION
POSITIVE REGULATION OF DNA DAMAGE RESPONSE, SIGNAL TRANSDUCTION BY P53 CLASS
POSITIVE REGULATION OF DNA DAMAGE RESPONSE, SIGNAL TRANSDUCTION BY P53 CLASS
POSITIVE REGULATION OF G2/M TRANSITION OF MITOTIC CELL CYCLE
POSITIVE REGULATION OF SIGNAL TRANSDUCTION BY P53 CLASS MEDIATOR
POSITIVE REGULATION OF SIGNAL TRANSDUCTION BY P53 CLASS MEDIATOR
SA_REG_CASCADE_OF_CYCLIN_EXPR
SA_REG_CASCADE_OF_CYCLIN_EXPR
SOMATIC STEM CELL DIVISION
DNA DEALKYLATION
DNA DEMETHYLATION
BIOCARTA_ATRBRCA_PATHWAY
BIOCARTA_ATRBRCA_PATHWAY
CELLULAR RESPONSE TO GAMMA RADIATION
DNA DOUBLE STRAND BREAK RESPONSE
DNA DOUBLE STRAND BREAK RESPONSE
DOUBLE-STRAND BREAK REPAIR VIA SYNTHESIS-DEPENDENT STRAND ANNEALING
DOUBLE-STRAND BREAK REPAIR VIA SYNTHESIS-DEPENDENT STRAND ANNEALING
DOUBLE-STRAND BREAK REPAIR VIA SYNTHESIS-DEPENDENT STRAND ANNEALING
G2 M DNA DAMAGE CHECKPOINT
G2 M DNA DAMAGE CHECKPOINT
NONHOMOLOGOUS END-JOINING (NHEJ)
NONHOMOLOGOUS END-JOINING (NHEJ)
POSITIVE REGULATION OF DNA REPAIR
RECRUITMENT AND ATM-MEDIATED PHOSPHORYLATION OF REPAIR AND SIGNALING PROTEIN
RECRUITMENT AND ATM-MEDIATED PHOSPHORYLATION OF REPAIR AND SIGNALING PROTEIN
RESOLUTION OF D-LOOP STRUCTURES THROUGH SYNTHESIS-DEPENDENT STRAND ANNEALING
RESOLUTION OF D-LOOP STRUCTURES THROUGH SYNTHESIS-DEPENDENT STRAND ANNEALING
RESOLUTION OF D-LOOP STRUCTURES THROUGH SYNTHESIS-DEPENDENT STRAND ANNEALING
NEGATIVE REGULATION OF CARTILAGE DEVELOPMENT
NEGATIVE REGULATION OF CHONDROCYTE DIFFERENTIATION
REGULATION OF CARTILAGE DEVELOPMENT
REGULATION OF CHONDROCYTE DIFFERENTIATION
BIOCARTA_CARM_ER_PATHWAY
BIOCARTA_HER2_PATHWAY
BIOCARTA_MTA3_PATHWAY
BMAL1:CLOCK,NPAS2 ACTIVATES CIRCADIAN GENE EXPRESSION
CELLULAR RESPONSE TO ALCOHOL
CELLULAR RESPONSE TO ESTRADIOL STIMULUS
CELLULAR RESPONSE TO ESTROGEN STIMULUS
CIRCADIAN CLOCK

CIRCADIAN CLOCK
INTRACELLULAR ESTROGEN RECEPTOR SIGNALING PATHWAY
INTRACELLULAR STEROID HORMONE RECEPTOR SIGNALING PATHWAY
INTRACELLULAR STEROID HORMONE RECEPTOR SIGNALING PATHWAY
INTRACELLULAR STEROID HORMONE RECEPTOR SIGNALING PATHWAY
NUCLEAR RECEPTOR TRANSCRIPTION PATHWAY
NUCLEAR RECEPTOR TRANSCRIPTION PATHWAY
NUCLEAR RECEPTOR TRANSCRIPTION PATHWAY
NUCLEAR SIGNALING BY ERBB4
RESPONSE TO ESTRADIOL
RORA ACTIVATES GENE EXPRESSION
SIGNALING EVENTS MEDIATED BY HDAC CLASS II
SIGNALING MEDIATED BY P38-ALPHA AND P38-BETA
CELLULAR RESPONSE TO DSRNA
CELLULAR RESPONSE TO DSRNA
CELLULAR RESPONSE TO EXOGENOUS DSRNA
DSRNA FRAGMENTATION
NEGATIVE REGULATION OF GENE SILENCING
POSTTRANSCRIPTIONAL GENE SILENCING BY RNA
POSTTRANSCRIPTIONAL GENE SILENCING BY RNA
POSTTRANSCRIPTIONAL GENE SILENCING
POSTTRANSCRIPTIONAL GENE SILENCING
PRODUCTION OF SMALL RNA INVOLVED IN GENE SILENCING BY RNA
REGULATION OF GENE SILENCING BY RNA
REGULATION OF GENE SILENCING
REGULATION OF POSTTRANSCRIPTIONAL GENE SILENCING
RNA INTERFERENCE
POSITIVE REGULATION OF MONOOXYGENASE ACTIVITY
POSITIVE REGULATION OF MONOOXYGENASE ACTIVITY
POSITIVE REGULATION OF NITRIC OXIDE BIOSYNTHETIC PROCESS
POSITIVE REGULATION OF NITRIC OXIDE METABOLIC PROCESS
POSITIVE REGULATION OF NITRIC-OXIDE SYNTHASE ACTIVITY
POSITIVE REGULATION OF NITRIC-OXIDE SYNTHASE ACTIVITY
POSITIVE REGULATION OF OXIDOREDUCTASE ACTIVITY
POSITIVE REGULATION OF OXIDOREDUCTASE ACTIVITY
POSITIVE REGULATION OF REACTIVE OXYGEN SPECIES BIOSYNTHETIC PROCESS
REGULATION OF MONOOXYGENASE ACTIVITY
REGULATION OF MONOOXYGENASE ACTIVITY
REGULATION OF NITRIC-OXIDE SYNTHASE ACTIVITY
REGULATION OF NITRIC-OXIDE SYNTHASE ACTIVITY
ACTIVIN RECEPTOR SIGNALING PATHWAY
DEVELOPMENT OF PRIMARY FEMALE SEXUAL CHARACTERISTICS
FEMALE GONAD DEVELOPMENT
NEGATIVE REGULATION OF CYTOKINE BIOSYNTHETIC PROCESS
NEGATIVE REGULATION OF INSULIN SECRETION
NEGATIVE REGULATION OF PEPTIDE HORMONE SECRETION
NEGATIVE REGULATION OF PEPTIDE SECRETION
OVARIAN FOLLICLE DEVELOPMENT
OVULATION CYCLE PROCESS
OVULATION CYCLE
POSITIVE REGULATION OF REPRODUCTIVE PROCESS

REGULATION OF ENDOCRINE PROCESS
SIGNALING BY ACTIVIN
CELLULAR RESPONSE TO CATECHOLAMINE STIMULUS
CELLULAR RESPONSE TO MONOAMINE STIMULUS
RESPONSE TO CATECHOLAMINE
RESPONSE TO MONOAMINE
FORMATION OF THE BETA-CATENIN:TCF TRANSACTIVATING COMPLEX
FORMATION OF THE BETA-CATENIN:TCF TRANSACTIVATING COMPLEX
REPRESSION OF WNT TARGET GENES
ACROSOME REACTION
ACTIN CYTOSKELETON REORGANIZATION
AMINO ACID AND OLIGOPEPTIDE SLC TRANSPORTERS
AMINO ACID TRANSPORT ACROSS THE PLASMA MEMBRANE
BIOCARTA_DNAFRAGMENT_PATHWAY
BIOCARTA_RARRXR_PATHWAY
BIOCARTA_SET_PATHWAY
BIOCARTA_VDR_PATHWAY
CELL RECOGNITION
CHROMOSOME SEPARATION
GLYCOPROTEIN HORMONES
INSULIN IGF PATHWAY-PROTEIN KINASE B SIGNALING CASCADE
MICROTUBULE ANCHORING
MITOCHONDRIAL RNA PROCESSING
MITOCHONDRIAL RNA PROCESSING
MYOBLAST DIFFERENTIATION
N-CADHERIN SIGNALING EVENTS
NEGATIVE REGULATION OF ESTABLISHMENT OF PROTEIN LOCALIZATION TO PLASMA MEMI
NEURONAL STEM CELL POPULATION MAINTENANCE
P38MAPK EVENTS
PEPTIDE HORMONE BIOSYNTHESIS
PHOSPHATIDYLINOSITOL 3-KINASE SIGNALING
PHOSPHATIDYLINOSITOL-3-PHOSPHATE BIOSYNTHETIC PROCESS
PHOSPHATIDYLINOSITOL-3-PHOSPHATE BIOSYNTHETIC PROCESS
POSITIVE REGULATION OF ANTIGEN RECEPTOR-MEDIATED SIGNALING PATHWAY
POSITIVE REGULATION OF GLYCOPROTEIN BIOSYNTHETIC PROCESS
POSITIVE REGULATION OF GLYCOPROTEIN METABOLIC PROCESS
POSITIVE REGULATION OF PROTEIN EXPORT FROM NUCLEUS
PROTEIN IMPORT INTO PEROXISOME MATRIX
PROTEIN K63-LINKED DEUBIQUITINATION
PROTEIN KINASE C SIGNALING
RAP PROTEIN SIGNAL TRANSDUCTION
REGULATION OF CELLULAR EXTRAVASATION
REGULATION OF HORMONE METABOLIC PROCESS
REGULATION OF MYOBLAST FUSION
REGULATION OF PROTEIN EXPORT FROM NUCLEUS
REGULATION OF PROTEIN EXPORT FROM NUCLEUS
REGULATION OF PROTEIN HOMOOIGOMERIZATION
SIGNALING EVENTS MEDIATED BY THE HEDGEHOG FAMILY
SMOOTH MUSCLE CELL DIFFERENTIATION
TISSUE REGENERATION
TRNA THREONYLCARBAMOYLADENOSINE METABOLIC PROCESS

TRNA THREONYLCARBAMOYLADENOSINE METABOLIC PROCESS

YAP1- AND WWTR1 (TAZ)-STIMULATED GENE EXPRESSION

ue used to create the enrichment map in Supplementary Figure 14. This value is $(ES - \min(ES)) / (\max(ES) - \min(ES))$

Database	Pathway ID	Enrichment Score (ES)	Standardized ES†	Gene
REACTOME DATABASE ID RELEASE 55	442755	0.4343	0.0554	ADCY3
GOBP	GO:0034199	0.5247	0.2721	ADCY3
GOBP	GO:0034199	0.5247	0.2721	ADCY9
REACTOME DATABASE ID RELEASE 55	170660	0.6199	0.5003	ADCY3
REACTOME DATABASE ID RELEASE 55	170660	0.6199	0.5003	ADCY9
REACTOME	R-HSA-170670.1	0.5521	0.3376	ADCY3
REACTOME	R-HSA-170670.1	0.5521	0.3376	ADCY9
GOBP	GO:0071880	0.4217	0.0252	ADCY9
GOBP	GO:0071880	0.4217	0.0252	PDE4D
GOBP	GO:0007189	0.4122	0.0024	PTHLH
GOBP	GO:0007189	0.4122	0.0024	ADCY3
GOBP	GO:0007189	0.4122	0.0024	ADCY9
GOBP	GO:0007189	0.4122	0.0024	PDE4D
GOBP	GO:0007193	0.4223	0.0266	MCHR1
GOBP	GO:0007193	0.4223	0.0266	ADCY3
GOBP	GO:0007193	0.4223	0.0266	ADCY9
GOBP	GO:0007193	0.4223	0.0266	CORT
GOBP	GO:0071875	0.4217	0.0252	ADCY9
GOBP	GO:0071875	0.4217	0.0252	PDE4D
REACTOME	R-HSA-111996.1	0.4310	0.0474	ADCY3
REACTOME	R-HSA-111996.1	0.4310	0.0474	ADCY9
REACTOME	R-HSA-111933.1	0.4216	0.0250	ADCY3
REACTOME	R-HSA-111933.1	0.4216	0.0250	ADCY9
REACTOME	R-HSA-111997.1	0.4216	0.0250	ADCY3
REACTOME	R-HSA-111997.1	0.4216	0.0250	ADCY9
GOBP	GO:0006171	0.4718	0.1453	ADCY3
GOBP	GO:0006171	0.4718	0.1453	ADCY9
GOBP	GO:0046058	0.5935	0.4371	PTHLH
GOBP	GO:0046058	0.5935	0.4371	ADCY3
GOBP	GO:0046058	0.5935	0.4371	ADCY9
GOBP	GO:0046058	0.5935	0.4371	PDE4D
GOBP	GO:0019933	0.4832	0.1726	ADCY3
GOBP	GO:0019933	0.4832	0.1726	ADCY9
GOBP	GO:0019933	0.4832	0.1726	PDE4D
GOBP	GO:0009187	0.4588	0.1141	PTHLH
GOBP	GO:0009187	0.4588	0.1141	ADCY3
GOBP	GO:0009187	0.4588	0.1141	ADCY9
GOBP	GO:0009187	0.4588	0.1141	PDE4D
GOBP	GO:0019935	0.4454	0.0819	ADCY3
GOBP	GO:0019935	0.4454	0.0819	ADCY9
GOBP	GO:0019935	0.4454	0.0819	PDE4D
REACTOME DATABASE ID RELEASE 55	1489509	0.4559	0.1072	ADCY3
REACTOME DATABASE ID RELEASE 55	1489509	0.4559	0.1072	ADCY9
REACTOME DATABASE ID RELEASE 55	212718	0.4683	0.1369	ADCY3
REACTOME DATABASE ID RELEASE 55	212718	0.4683	0.1369	ADCY9
PANTHER PATHWAY	P00019	0.4392	0.0670	ADCY3
PANTHER PATHWAY	P00019	0.4392	0.0670	ADCY9

REACTOME DATABASE ID RELEASE 55	112040	0.4310	0.0474	ADCY3
REACTOME DATABASE ID RELEASE 55	112040	0.4310	0.0474	ADCY9
REACTOME DATABASE ID RELEASE 55	997269	0.5521	0.3376	ADCY3
REACTOME DATABASE ID RELEASE 55	997269	0.5521	0.3376	ADCY9
PATHWAY INTERACTION DATABASE NCI-NA LPA4-MEDIATED 5		0.5537	0.3415	ADCY3
PATHWAY INTERACTION DATABASE NCI-NA LPA4-MEDIATED 5		0.5537	0.3415	ADCY9
GOBP	GO:1903523	0.4744	0.1515	PDE4D
REACTOME	R-HSA-5654219.1	0.4569	0.1094	ADCY3
REACTOME	R-HSA-5654219.1	0.4569	0.1094	ADCY9
REACTOME	R-HSA-5654221.1	0.4192	0.0193	ADCY3
REACTOME	R-HSA-5654221.1	0.4192	0.0193	ADCY9
REACTOME	R-HSA-5654227.1	0.4425	0.0750	ADCY3
REACTOME	R-HSA-5654227.1	0.4425	0.0750	ADCY9
REACTOME DATABASE ID RELEASE 55	5654228	0.4150	0.0091	ADCY3
REACTOME DATABASE ID RELEASE 55	5654228	0.4150	0.0091	ADCY9
REACTOME	R-HSA-164378.1	0.4943	0.1992	ADCY3
REACTOME	R-HSA-164378.1	0.4943	0.1992	ADCY9
REACTOME DATABASE ID RELEASE 55	163615	0.4478	0.0877	ADCY3
REACTOME DATABASE ID RELEASE 55	163615	0.4478	0.0877	ADCY9
REACTOME DATABASE ID RELEASE 55	111931	0.4419	0.0737	ADCY3
REACTOME DATABASE ID RELEASE 55	111931	0.4419	0.0737	ADCY9
REACTOME	R-HSA-112043.1	0.4219	0.0255	ADCY3
REACTOME	R-HSA-112043.1	0.4219	0.0255	ADCY9
REACTOME DATABASE ID RELEASE 55	167021	0.4450	0.0810	ADCY3
REACTOME DATABASE ID RELEASE 55	167021	0.4450	0.0810	ADCY9
REACTOME DATABASE ID RELEASE 55	1251932	0.4736	0.1496	ADCY3
REACTOME DATABASE ID RELEASE 55	1251932	0.4736	0.1496	ADCY9
GOBP	GO:0032743	0.4614	0.1202	PDE4D
REACTOME DATABASE ID RELEASE 55	438064	0.4256	0.0346	ADCY3
GOBP	GO:0009154	0.5344	0.2953	PDE4D
GOBP	GO:0072523	0.4459	0.0831	AOX1
GOBP	GO:0072523	0.4459	0.0831	PDE4D
GOBP	GO:0086004	0.4661	0.1315	PDE4D
GOBP	GO:0010649	0.4786	0.1615	PDE4D
GOBP	GO:0010880	0.4741	0.1507	PDE4D
GOBP	GO:0009261	0.5100	0.2368	PDE4D
GOBP	GO:0034332	0.4359	0.0593	CDH2
REACTOME	R-HSA-418990.2	0.5433	0.3166	CDH2
GOBP	GO:0097296	0.4650	0.1290	CASP8
GOBP	GO:0097296	0.4650	0.1290	CFLAR
GOBP	GO:0006309	0.4490	0.0906	DFFA
MSIGDB_C2	BIOCARTA_CASP8	0.4325	0.0510	DFFA
MSIGDB_C2	BIOCARTA_CASP8	0.4325	0.0510	CASP8
MSIGDB_C2	BIOCARTA_DEATH	0.4502	0.0934	DFFA
MSIGDB_C2	BIOCARTA_DEATH	0.4502	0.0934	CASP8
MSIGDB_C2	BIOCARTA_DEATH	0.4502	0.0934	CFLAR
MSIGDB_C2	BIOCARTA_FAS_P	0.4661	0.1315	DFFA
MSIGDB_C2	BIOCARTA_FAS_P	0.4661	0.1315	CASP8
MSIGDB_C2	BIOCARTA_FAS_P	0.4661	0.1315	CFLAR
MSIGDB_C2	BIOCARTA_SODD	0.4379	0.0640	CASP8
REACTOME DATABASE ID RELEASE 55	5218900	0.4860	0.1793	CASP8

REACTOME DATABASE ID RELEASE 55	69416	0.4860	0.1793	CASP8
GOBP	GO:0001701	0.4212	0.0239	CASP8
GOBP	GO:0030225	0.5281	0.2802	CASP8
GOBP	GO:2001240	0.5273	0.2784	TERT
GOBP	GO:0010832	0.4220	0.0260	CFLAR
GOBP	GO:1901099	0.5273	0.2784	TERT
GOBP	GO:0051154	0.4127	0.0035	CFLAR
GOBP	GO:2001269	0.4279	0.0401	CASP8
GOBP	GO:2001269	0.4279	0.0401	CFLAR
REACTOME	R-HSA-3371378.1	0.4860	0.1793	CASP8
GOBP	GO:1900117	0.4943	0.1993	DFFA
GOBP	GO:1900117	0.4943	0.1993	CDKN2A
GOBP	GO:2001239	0.4922	0.1941	TERT
GOBP	GO:0045649	0.4404	0.0701	CASP8
MSIGDB_C2	SA_CASPASE_CAS	0.5552	0.3451	DFFA
MSIGDB_C2	SA_CASPASE_CAS	0.5552	0.3451	CASP8
REACTOME	R-HSA-5357786.2	0.4783	0.1608	CASP8
PATHWAY INTERACTION DATABASE NCI-NA TRAIL SIGNALING		0.4312	0.0480	CASP8
PATHWAY INTERACTION DATABASE NCI-NA TRAIL SIGNALING		0.4312	0.0480	CFLAR
REACTOME DATABASE ID RELEASE 55	2562578	0.4260	0.0353	CASP8
MSIGDB_C2	BIOCARTA_ACH_F	0.5688	0.3778	TERT
MSIGDB_C2	BIOCARTA_TEL_P	0.6706	0.6217	TERT
GOBP	GO:0007569	0.4542	0.1031	TERT
GOBP	GO:0007569	0.4542	0.1031	CDKN2A
GOBP	GO:0007569	0.4542	0.1031	ATM
GOBP	GO:0070199	0.6937	0.6773	TERT
GOBP	GO:0070199	0.6937	0.6773	BRCA2
REACTOME DATABASE ID RELEASE 55	180786	0.4875	0.1829	TERT
GOBP	GO:0070828	0.5417	0.3128	CDKN2A
GOBP	GO:0090344	0.6567	0.5885	TERT
GOBP	GO:0070198	0.6490	0.5701	TERT
GOBP	GO:0070198	0.6490	0.5701	BRCA2
GOBP	GO:0090342	0.5290	0.2824	TERT
GOBP	GO:0090342	0.5290	0.2824	CDKN2A
GOBP	GO:2000772	0.5862	0.4195	TERT
GOBP	GO:2000772	0.5862	0.4195	CDKN2A
GOBP	GO:1902893	0.6356	0.5379	TERT
GOBP	GO:0090399	0.8284	1.0000	TERT
GOBP	GO:0090399	0.8284	1.0000	CDKN2A
GOBP	GO:0090399	0.8284	1.0000	ATM
GOBP	GO:0006278	0.5843	0.4150	TERT
GOBP	GO:0006278	0.5843	0.4150	ATM
GOBP	GO:0007004	0.6456	0.5618	TERT
GOBP	GO:0007004	0.6456	0.5618	ATM
REACTOME DATABASE ID RELEASE 55	157579	0.4177	0.0155	TERT
MSIGDB_C2	BIOCARTA_G1_P	0.4355	0.0581	CDKN2A
MSIGDB_C2	BIOCARTA_G1_P	0.4355	0.0581	ATM
MSIGDB_C2	BIOCARTA_G1_P	0.4355	0.0581	CCNE1
MSIGDB_C2	BIOCARTA_P53_P	0.4658	0.1309	ATM
MSIGDB_C2	BIOCARTA_P53_P	0.4658	0.1309	CCNE1
PANTHER PATHWAY	P00013	0.4198	0.0205	CCNE1

PATHWAY INTERACTION DATABASE NCI-NA FOXM1 TRANSCRI		0.4407	0.0708	ESR1
PATHWAY INTERACTION DATABASE NCI-NA FOXM1 TRANSCRI		0.4407	0.0708	CDKN2A
PATHWAY INTERACTION DATABASE NCI-NA FOXM1 TRANSCRI		0.4407	0.0708	BRCA2
PATHWAY INTERACTION DATABASE NCI-NA FOXM1 TRANSCRI		0.4407	0.0708	CCNE1
GOBP	GO:0031572	0.5234	0.2690	BABAM1
GOBP	GO:0031572	0.5234	0.2690	ATM
GOBP	GO:0044818	0.4708	0.1428	ATM
GOBP	GO:0050869	0.4305	0.0463	CDKN2A
GOBP	GO:0050869	0.4305	0.0463	ATM
GOBP	GO:0010972	0.4125	0.0031	ATM
GOBP	GO:1902751	0.4123	0.0026	RAD51B
GOBP	GO:0043517	0.5451	0.3210	CDKN2A
GOBP	GO:0043517	0.5451	0.3210	ATM
GOBP	GO:0010971	0.4602	0.1173	RAD51B
GOBP	GO:1901798	0.4790	0.1625	CDKN2A
GOBP	GO:1901798	0.4790	0.1625	ATM
MSIGDB_C2	SA_REG_CASCADI	0.5062	0.2278	CDKN2A
MSIGDB_C2	SA_REG_CASCADI	0.5062	0.2278	CCNE1
GOBP	GO:0048103	0.4686	0.1377	CDKN2A
GOBP	GO:0035510	0.4665	0.1324	FTO
GOBP	GO:0080111	0.4312	0.0478	FTO
MSIGDB_C2	BIOCARTA_ATRBF	0.4567	0.1090	ATM
MSIGDB_C2	BIOCARTA_ATRBF	0.4567	0.1090	BRCA2
GOBP	GO:0071480	0.4696	0.1401	ATM
REACTOME DATABASE ID RELEASE 55	5693606	0.4353	0.0577	BABAM1
REACTOME DATABASE ID RELEASE 55	5693606	0.4353	0.0577	ATM
GOBP	GO:0045003	0.4201	0.0214	ATM
GOBP	GO:0045003	0.4201	0.0214	BRCA2
GOBP	GO:0045003	0.4201	0.0214	RAD51B
REACTOME	R-HSA-69473.2	0.4241	0.0309	BABAM1
REACTOME	R-HSA-69473.2	0.4241	0.0309	ATM
REACTOME	R-HSA-5693571.1	0.4639	0.1264	BABAM1
REACTOME	R-HSA-5693571.1	0.4639	0.1264	ATM
GOBP	GO:0045739	0.4394	0.0675	BABAM1
REACTOME	R-HSA-5693565.1	0.4405	0.0703	BABAM1
REACTOME	R-HSA-5693565.1	0.4405	0.0703	ATM
REACTOME DATABASE ID RELEASE 55	5693554	0.4355	0.0583	ATM
REACTOME DATABASE ID RELEASE 55	5693554	0.4355	0.0583	BRCA2
REACTOME DATABASE ID RELEASE 55	5693554	0.4355	0.0583	RAD51B
GOBP	GO:0061037	0.5215	0.2643	PTHLH
GOBP	GO:0032331	0.5077	0.2314	PTHLH
GOBP	GO:0061035	0.4875	0.1829	PTHLH
GOBP	GO:0032330	0.4995	0.2117	PTHLH
MSIGDB_C2	BIOCARTA_CARM	0.4438	0.0781	ESR1
MSIGDB_C2	BIOCARTA_HER2_	0.4821	0.1698	ESR1
MSIGDB_C2	BIOCARTA_MTA3	0.4838	0.1741	ESR1
REACTOME	R-HSA-1368108.1	0.5209	0.2630	NCOA1
GOBP	GO:0097306	0.4181	0.0166	ESR1
GOBP	GO:0071392	0.5780	0.3998	ESR1
GOBP	GO:0071391	0.4833	0.1728	ESR1
REACTOME	R-HSA-400253.1	0.4437	0.0779	NCOA1

REACTOME	R-HSA-400253.1	0.4437	0.0779	PPP1CB
GOBP	GO:0030520	0.5593	0.3550	ESR1
GOBP	GO:0030518	0.4217	0.0251	ESR1
GOBP	GO:0030518	0.4217	0.0251	CCNE1
GOBP	GO:0030518	0.4217	0.0251	NCOA1
REACTOME	R-HSA-383280.1	0.4767	0.1569	ESR1
REACTOME	R-HSA-383280.1	0.4767	0.1569	NR2F6
REACTOME	R-HSA-383280.1	0.4767	0.1569	HNF4G
REACTOME DATABASE ID RELEASE 55	1251985	0.4518	0.0973	ESR1
GOBP	GO:0032355	0.4796	0.1640	ESR1
REACTOME	R-HSA-1368082.1	0.5497	0.3319	NCOA1
PATHWAY INTERACTION DATABASE NCI-NA SIGNALING EVENT		0.5074	0.2305	ESR1
PATHWAY INTERACTION DATABASE NCI-NA SIGNALING MEDI		0.4406	0.0705	ESR1
GOBP	GO:0071359	0.4562	0.1079	TERT
GOBP	GO:0071359	0.4562	0.1079	RALB
GOBP	GO:0071360	0.4569	0.1096	RALB
GOBP	GO:0031050	0.5095	0.2356	TERT
GOBP	GO:0060969	0.6892	0.6664	TERT
GOBP	GO:0035194	0.4124	0.0028	TERT
GOBP	GO:0035194	0.4124	0.0028	TNRC6B
GOBP	GO:0016441	0.4112	0.0000	TERT
GOBP	GO:0016441	0.4112	0.0000	TNRC6B
GOBP	GO:0070918	0.5095	0.2356	TERT
GOBP	GO:0060966	0.6605	0.5975	TERT
GOBP	GO:0060968	0.5325	0.2909	TERT
GOBP	GO:0060147	0.6605	0.5975	TERT
GOBP	GO:0016246	0.6554	0.5855	TERT
GOBP	GO:0032770	0.6466	0.5642	TERT
GOBP	GO:0032770	0.6466	0.5642	ESR1
GOBP	GO:0045429	0.4481	0.0885	ESR1
GOBP	GO:1904407	0.4481	0.0885	ESR1
GOBP	GO:0051000	0.7346	0.7752	TERT
GOBP	GO:0051000	0.7346	0.7752	ESR1
GOBP	GO:0051353	0.5059	0.2270	TERT
GOBP	GO:0051353	0.5059	0.2270	ESR1
GOBP	GO:1903428	0.4215	0.0247	ESR1
GOBP	GO:0032768	0.4148	0.0086	TERT
GOBP	GO:0032768	0.4148	0.0086	ESR1
GOBP	GO:0050999	0.4699	0.1406	TERT
GOBP	GO:0050999	0.4699	0.1406	ESR1
GOBP	GO:0032924	0.5005	0.2140	INHBB
GOBP	GO:0046545	0.4333	0.0530	INHBB
GOBP	GO:0008585	0.4333	0.0530	INHBB
GOBP	GO:0042036	0.5133	0.2446	INHBB
GOBP	GO:0046676	0.4505	0.0941	INHBB
GOBP	GO:0090278	0.4322	0.0504	INHBB
GOBP	GO:0002792	0.4126	0.0034	INHBB
GOBP	GO:0001541	0.4579	0.1120	INHBB
GOBP	GO:0022602	0.4414	0.0724	INHBB
GOBP	GO:0042698	0.4182	0.0167	INHBB
GOBP	GO:2000243	0.4991	0.2106	INHBB

GOBP	GO:0044060	0.4149	0.0088	INHBB
REACTOME DATABASE ID RELEASE 55	1502540	0.5210	0.2631	INHBB
GOBP	GO:0071870	0.4291	0.0429	PDE4D
GOBP	GO:0071868	0.4291	0.0429	PDE4D
GOBP	GO:0071869	0.4291	0.0429	PDE4D
GOBP	GO:0071867	0.4291	0.0429	PDE4D
REACTOME	R-HSA-201722.2	0.4371	0.0620	TERT
REACTOME	R-HSA-201722.2	0.4371	0.0620	TCF7L2
REACTOME DATABASE ID RELEASE 55	4641265	0.4123	0.0027	TCF7L2
GOBP	GO:0007340	0.4709	0.1432	ADCY3
GOBP	GO:0031532	0.4347	0.0564	FRY
REACTOME	R-HSA-425374.1	0.4182	0.0167	SLC6A18
REACTOME DATABASE ID RELEASE 55	352230	0.5339	0.2940	SLC6A18
MSIGDB_C2	BIOCARTA_DNAFI	0.5028	0.2196	DFFA
MSIGDB_C2	BIOCARTA_RARR>	0.4764	0.1562	NCOA1
MSIGDB_C2	BIOCARTA_SET_P	0.4608	0.1188	DFFA
MSIGDB_C2	BIOCARTA_VDR_F	0.4843	0.1751	NCOA1
GOBP	GO:0008037	0.4248	0.0325	KCNU1
GOBP	GO:0051304	0.4932	0.1966	APITD1
REACTOME DATABASE ID RELEASE 55	209822	0.4456	0.0825	INHBB
PANTHER PATHWAY	P00033	0.4207	0.0227	MDM4
GOBP	GO:0034453	0.4252	0.0336	PEX14
GOBP	GO:0000963	0.5413	0.3119	GTPBP3
GOBP	GO:0000963	0.5413	0.3119	TRMT61B
GOBP	GO:0045445	0.5165	0.2523	TCF7L2
PATHWAY INTERACTION DATABASE NCI-NA N-CADHERIN SIGN		0.4122	0.0024	CDH2
GOBP	GO:0090005	0.4264	0.0363	ANXA13
GOBP	GO:0097150	0.5715	0.3843	CDH2
REACTOME DATABASE ID RELEASE 55	171007	0.4664	0.1323	RALB
REACTOME DATABASE ID RELEASE 55	209952	0.4670	0.1338	INHBB
GOBP	GO:0014065	0.4647	0.1281	PIK3C2B
GOBP	GO:0036092	0.6415	0.5520	PIK3C2B
GOBP	GO:0036092	0.6415	0.5520	ATM
GOBP	GO:0050857	0.4366	0.0608	KCNN4
GOBP	GO:0010560	0.4915	0.1924	TCF7L2
GOBP	GO:1903020	0.4440	0.0786	TCF7L2
GOBP	GO:0046827	0.5167	0.2529	TCF7L2
GOBP	GO:0016558	0.4646	0.1280	PEX14
GOBP	GO:0070536	0.5459	0.3228	BABAM1
GOBP	GO:0070528	0.4710	0.1434	PLVAP
GOBP	GO:0032486	0.4819	0.1695	SGSM3
GOBP	GO:0002691	0.5444	0.3194	PLVAP
GOBP	GO:0032350	0.4184	0.0172	TCF7L2
GOBP	GO:1901739	0.4467	0.0852	CFLAR
GOBP	GO:0046825	0.5059	0.2271	CDKN2A
GOBP	GO:0046825	0.5059	0.2271	TCF7L2
GOBP	GO:0032462	0.5224	0.2666	PEX14
PATHWAY INTERACTION DATABASE NCI-NA SIGNALING EVEN1		0.4896	0.1880	PTHLH
GOBP	GO:0051145	0.4252	0.0336	MKL1
GOBP	GO:0042246	0.4795	0.1637	CFLAR
GOBP	GO:0070525	0.5931	0.4360	GTPBP3

GOBP	GO:0070525	0.5931	0.4360	TRMT61B
REACTOME DATABASE ID RELEASE 55	2032785	0.4338	0.0543	NCOA1

)-min(ES))

Number of SNPs in gene	SNP with lowest P-value	P-value	Distance to gene from SNP (bp)	Appears in Supplementary Figure 14
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
8,270	5_58429733_C_T	1.7×10^{-8}	0	Yes
1,366	12_28174817_C_T	2.3×10^{-31}	49901	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
8,270	5_58429733_C_T	1.7×10^{-8}	0	Yes
427	22_41059171_A_G	7.7×10^{-12}	16010	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
56	1_10506667_G_A	1.7×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
8,270	5_58429733_C_T	1.7×10^{-8}	0	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
1,366	12_28174817_C_T	2.3×10^{-31}	49901	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
8,270	5_58429733_C_T	1.7×10^{-8}	0	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
8,270	5_58429733_C_T	1.7×10^{-8}	0	Yes
1,366	12_28174817_C_T	2.3×10^{-31}	49901	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
8,270	5_58429733_C_T	1.7×10^{-8}	0	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
8,270	5_58429733_C_T	1.7×10^{-8}	0	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes

836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
8,270	5_58429733_C_T	1.7×10^{-8}	0	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
1,630	16_4106788_C_A	1.4×10^{-8}	0	Yes
8,270	5_58429733_C_T	1.7×10^{-8}	0	Yes
836	2_25129473_A_G	1.3×10^{-8}	0	Yes
8,270	5_58429733_C_T	1.7×10^{-8}	0	Yes
570	2_201524267_A_C	5.4×10^{-10}	0	Yes
8,270	5_58429733_C_T	1.7×10^{-8}	0	Yes
8,270	5_58429733_C_T	1.7×10^{-8}	0	Yes
8,270	5_58429733_C_T	1.7×10^{-8}	0	Yes
8,270	5_58429733_C_T	1.7×10^{-8}	0	Yes
8,270	5_58429733_C_T	1.7×10^{-8}	0	Yes
5,742	18_25401204_AT_A	1.4×10^{-8}	129725	
5,742	18_25401204_AT_A	1.4×10^{-8}	129725	
321	2_202122995_A_G	3.2×10^{-11}	0	
323	2_202004837_G_C	3.1×10^{-9}	0	
112	1_10537437_C_G	2.0×10^{-20}	0	
112	1_10537437_C_G	2.0×10^{-20}	0	
321	2_202122995_A_G	3.2×10^{-11}	0	
112	1_10537437_C_G	2.0×10^{-20}	0	
321	2_202122995_A_G	3.2×10^{-11}	0	
323	2_202004837_G_C	3.1×10^{-9}	0	
112	1_10537437_C_G	2.0×10^{-20}	0	
321	2_202122995_A_G	3.2×10^{-11}	0	
323	2_202004837_G_C	3.1×10^{-9}	0	
321	2_202122995_A_G	3.2×10^{-11}	0	
321	2_202122995_A_G	3.2×10^{-11}	0	

321	2_202122995_A_G	3.2×10^{-11}	0
321	2_202122995_A_G	3.2×10^{-11}	0
321	2_202122995_A_G	3.2×10^{-11}	0
381	5_1279790_C_T	1.9×10^{-49}	0
323	2_202004837_G_C	3.1×10^{-9}	0
381	5_1279790_C_T	1.9×10^{-49}	0
323	2_202004837_G_C	3.1×10^{-9}	0
321	2_202122995_A_G	3.2×10^{-11}	0
323	2_202004837_G_C	3.1×10^{-9}	0
321	2_202122995_A_G	3.2×10^{-11}	0
112	1_10537437_C_G	2.0×10^{-20}	0
170	9_21963048_C_T	4.3×10^{-15}	0
381	5_1279790_C_T	1.9×10^{-49}	0
321	2_202122995_A_G	3.2×10^{-11}	0
112	1_10537437_C_G	2.0×10^{-20}	0
321	2_202122995_A_G	3.2×10^{-11}	0
321	2_202122995_A_G	3.2×10^{-11}	0
321	2_202122995_A_G	3.2×10^{-11}	0
323	2_202004837_G_C	3.1×10^{-9}	0
321	2_202122995_A_G	3.2×10^{-11}	0
381	5_1279790_C_T	1.9×10^{-49}	0
381	5_1279790_C_T	1.9×10^{-49}	0
381	5_1279790_C_T	1.9×10^{-49}	0
170	9_21963048_C_T	4.3×10^{-15}	0
701	11_108098459_TAA_T	2.5×10^{-12}	0
381	5_1279790_C_T	1.9×10^{-49}	0
485	13_32972626_A_T	2.5×10^{-11}	0
381	5_1279790_C_T	1.9×10^{-49}	0
170	9_21963048_C_T	4.3×10^{-15}	0
381	5_1279790_C_T	1.9×10^{-49}	0
381	5_1279790_C_T	1.9×10^{-49}	0
485	13_32972626_A_T	2.5×10^{-11}	0
381	5_1279790_C_T	1.9×10^{-49}	0
170	9_21963048_C_T	4.3×10^{-15}	0
381	5_1279790_C_T	1.9×10^{-49}	0
170	9_21963048_C_T	4.3×10^{-15}	0
381	5_1279790_C_T	1.9×10^{-49}	0
170	9_21963048_C_T	4.3×10^{-15}	0
701	11_108098459_TAA_T	2.5×10^{-12}	0
381	5_1279790_C_T	1.9×10^{-49}	0
701	11_108098459_TAA_T	2.5×10^{-12}	0
381	5_1279790_C_T	1.9×10^{-49}	0
701	11_108098459_TAA_T	2.5×10^{-12}	0
381	5_1279790_C_T	1.9×10^{-49}	0
170	9_21963048_C_T	4.3×10^{-15}	0
701	11_108098459_TAA_T	2.5×10^{-12}	0
755	19_30277729_C_T	6.8×10^{-9}	25171
701	11_108098459_TAA_T	2.5×10^{-12}	0
755	19_30277729_C_T	6.8×10^{-9}	25171
755	19_30277729_C_T	6.8×10^{-9}	25171

2,783	6_151985574_T_C	8.9×10^{-39}	26056
170	9_21963048_C_T	4.3×10^{-15}	0
485	13_32972626_A_T	2.5×10^{-11}	0
755	19_30277729_C_T	6.8×10^{-9}	25171
141	19_17393925_C_A	4.7×10^{-53}	0
701	11_108098459_TAA_T	2.5×10^{-12}	0
701	11_108098459_TAA_T	2.5×10^{-12}	0
170	9_21963048_C_T	4.3×10^{-15}	0
701	11_108098459_TAA_T	2.5×10^{-12}	0
701	11_108098459_TAA_T	2.5×10^{-12}	0
4,358	14_69029203_C_T	1.1×10^{-10}	0
170	9_21963048_C_T	4.3×10^{-15}	0
701	11_108098459_TAA_T	2.5×10^{-12}	0
4,358	14_69029203_C_T	1.1×10^{-10}	0
170	9_21963048_C_T	4.3×10^{-15}	0
701	11_108098459_TAA_T	2.5×10^{-12}	0
170	9_21963048_C_T	4.3×10^{-15}	0
755	19_30277729_C_T	6.8×10^{-9}	25171
170	9_21963048_C_T	4.3×10^{-15}	0
3,106	16_53809123_C_T	6.0×10^{-14}	0
3,106	16_53809123_C_T	6.0×10^{-14}	0
701	11_108098459_TAA_T	2.5×10^{-12}	0
485	13_32972626_A_T	2.5×10^{-11}	0
701	11_108098459_TAA_T	2.5×10^{-12}	0
141	19_17393925_C_A	4.7×10^{-53}	0
701	11_108098459_TAA_T	2.5×10^{-12}	0
701	11_108098459_TAA_T	2.5×10^{-12}	0
485	13_32972626_A_T	2.5×10^{-11}	0
4,358	14_69029203_C_T	1.1×10^{-10}	0
141	19_17393925_C_A	4.7×10^{-53}	0
701	11_108098459_TAA_T	2.5×10^{-12}	0
141	19_17393925_C_A	4.7×10^{-53}	0
701	11_108098459_TAA_T	2.5×10^{-12}	0
141	19_17393925_C_A	4.7×10^{-53}	0
141	19_17393925_C_A	4.7×10^{-53}	0
701	11_108098459_TAA_T	2.5×10^{-12}	0
701	11_108098459_TAA_T	2.5×10^{-12}	0
485	13_32972626_A_T	2.5×10^{-11}	0
4,358	14_69029203_C_T	1.1×10^{-10}	0
1,366	12_28174817_C_T	2.3×10^{-31}	49901
1,366	12_28174817_C_T	2.3×10^{-31}	49901
1,366	12_28174817_C_T	2.3×10^{-31}	49901
1,366	12_28174817_C_T	2.3×10^{-31}	49901
2,783	6_151985574_T_C	8.9×10^{-39}	26056
2,783	6_151985574_T_C	8.9×10^{-39}	26056
2,783	6_151985574_T_C	8.9×10^{-39}	26056
1,426	2_24739694_C_CT	9.7×10^{-9}	67651
2,783	6_151985574_T_C	8.9×10^{-39}	26056
2,783	6_151985574_T_C	8.9×10^{-39}	26056
2,783	6_151985574_T_C	8.9×10^{-39}	26056
1,426	2_24739694_C_CT	9.7×10^{-9}	67651

[illegible]

605	2_121079515_A_C	9.3×10^{-18}	24203
605	2_121079515_A_C	9.3×10^{-18}	24203
8,270	5_58429733_C_T	1.7×10^{-8}	0
8,270	5_58429733_C_T	1.7×10^{-8}	0
8,270	5_58429733_C_T	1.7×10^{-8}	0
8,270	5_58429733_C_T	1.7×10^{-8}	0
381	5_1279790_C_T	1.9×10^{-49}	0
2,437	10_114782803_T_C	6.5×10^{-15}	0
2,437	10_114782803_T_C	6.5×10^{-15}	0
836	2_25129473_A_G	1.3×10^{-8}	0
1,573	927_CAATAAATAAATA_C/	2.0×10^{-12}	0
290	5_1241565_A_G	8.4×10^{-13}	0
290	5_1241565_A_G	8.4×10^{-13}	0
112	1_10537437_C_G	2.0×10^{-20}	0
1,426	2_24739694_C_CT	9.7×10^{-9}	67651
112	1_10537437_C_G	2.0×10^{-20}	0
1,426	2_24739694_C_CT	9.7×10^{-9}	67651
3,952	8_36849946_C_G	2.8×10^{-12}	56303
154	10491895_A_AGCGAGAC1	4.6×10^{-9}	0
605	2_121079515_A_C	9.3×10^{-18}	24203
527	1_204518842_C_A	7.0×10^{-26}	0
813	1_10566272_C_T	9.7×10^{-22}	0
118	19_17456375_TCTC_T	1.4×10^{-23}	0
217	2_29094032_C_A	8.6×10^{-9}	0
2,437	10_114782803_T_C	6.5×10^{-15}	0
5,742	18_25401204_AT_A	1.4×10^{-8}	129725
541	8_124757661_C_T	1.7×10^{-11}	8014
5,742	18_25401204_AT_A	1.4×10^{-8}	129725
447	2_121077184_A_G	1.2×10^{-13}	24898
605	2_121079515_A_C	9.3×10^{-18}	24203
533	1_204464181_C_T	1.0×10^{-24}	0
533	1_204464181_C_T	1.0×10^{-24}	0
701	11_108098459_TAA_T	2.5×10^{-12}	0
182	19_44281824_C_CTCTT	2.7×10^{-9}	0
2,437	10_114782803_T_C	6.5×10^{-15}	0
2,437	10_114782803_T_C	6.5×10^{-15}	0
2,437	10_114782803_T_C	6.5×10^{-15}	0
813	1_10566272_C_T	9.7×10^{-22}	0
141	19_17393925_C_A	4.7×10^{-53}	0
308	19_17462094_T_G	1.3×10^{-26}	0
196	22_40810946_T_C	1.6×10^{-11}	0
308	19_17462094_T_G	1.3×10^{-26}	0
2,437	10_114782803_T_C	6.5×10^{-15}	0
323	2_202004837_G_C	3.1×10^{-9}	0
170	9_21963048_C_T	4.3×10^{-15}	0
2,437	10_114782803_T_C	6.5×10^{-15}	0
813	1_10566272_C_T	9.7×10^{-22}	0
1,366	12_28174817_C_T	2.3×10^{-31}	49901
1,176	22_40904707_CT_C	4.0×10^{-13}	0
323	2_202004837_G_C	3.1×10^{-9}	0
118	19_17456375_TCTC_T	1.4×10^{-23}	0

217

2_29094032_C_A

8.6x10⁻⁹

0

1,426

2_24739694_C_CT

9.7x10⁻⁹

67651

Supplementary Table 13: Detailed information about themes and unique genes appearing in the enrichment maps (Supplementary Fig

Theme	Gene	Number of SNPs in gene	SNP with lowest P-value	P-value	Distance to gene from SNP (bp)
ADENYLATE CYCLASE	PTHLH	1,366	12_28174817_C_T	2.3x10 ⁻³¹	49901
ADENYLATE CYCLASE	MCHR1	427	22_41059171_A_G	7.6x10 ⁻¹²	16010
ADENYLATE CYCLASE	AOX1	570	2_201524267_A_C	5.4x10 ⁻¹⁰	0
ADENYLATE CYCLASE	ADCY3	836	2_25129473_A_G	1.3x10 ⁻⁸	0
ADENYLATE CYCLASE	ADCY9	1,630	16_4106788_C_A	1.4x10 ⁻⁸	0
ADENYLATE CYCLASE	PDE4D	8,270	5_58429733_C_T	1.7x10 ⁻⁸	0
ADENYLATE CYCLASE	CORT	56	1_10506667_G_A	1.7x10 ⁻⁸	0
ADHERENS JUNCTION	CDH2	5,742	18_25401204_AT_A	1.4x10 ⁻⁸	129725
APOPTOSIS	TERT	381	5_1279790_C_T	1.9x10 ⁻⁴⁹	0
APOPTOSIS	DFFA	112	1_10537437_C_G	2.0x10 ⁻²⁰	0
APOPTOSIS	CDKN2A	170	9_21963048_C_T	4.3x10 ⁻¹⁵	0
APOPTOSIS	CASP8	321	2_202122995_A_G	3.2x10 ⁻¹¹	0
APOPTOSIS	CFLAR	323	2_202004837_G_C	3.1x10 ⁻⁹	0
CELL AGING/TELOMERE	TERT	381	5_1279790_C_T	1.9x10 ⁻⁴⁹	0
CELL AGING/TELOMERE	CDKN2A	170	9_21963048_C_T	4.3x10 ⁻¹⁵	0
CELL AGING/TELOMERE	ATM	701	11_108098459_TAA_T	2.5x10 ⁻¹²	0
CELL AGING/TELOMERE	BRCA2	485	13_32972626_A_T	2.5x10 ⁻¹¹	0
CELL CYCLE/DNA DAMAGE RESPONSE	BABAM1	141	19_17393925_C_A	4.7x10 ⁻⁵³	0
CELL CYCLE/DNA DAMAGE RESPONSE	ESR1	2,783	6_151985574_T_C	8.9x10 ⁻³⁹	26056
CELL CYCLE/DNA DAMAGE RESPONSE	CDKN2A	170	9_21963048_C_T	4.3x10 ⁻¹⁵	0
CELL CYCLE/DNA DAMAGE RESPONSE	ATM	701	11_108098459_TAA_T	2.5x10 ⁻¹²	0
CELL CYCLE/DNA DAMAGE RESPONSE	BRCA2	485	13_32972626_A_T	2.5x10 ⁻¹¹	0
CELL CYCLE/DNA DAMAGE RESPONSE	RAD51B	4,358	14_69029203_C_T	1.1x10 ⁻¹⁰	0
CELL CYCLE/DNA DAMAGE RESPONSE	CCNE1	755	19_30277729_C_T	6.8x10 ⁻⁹	25171
DNA DEMETHYLATION/DEALKYLATION	FTO	3,106	16_53809123_C_T	6.0x10 ⁻¹⁴	0
DOUBLE STRAND BREAK REPAIR	BABAM1	141	19_17393925_C_A	4.7x10 ⁻⁵³	0
DOUBLE STRAND BREAK REPAIR	ATM	701	11_108098459_TAA_T	2.5x10 ⁻¹²	0
DOUBLE STRAND BREAK REPAIR	BRCA2	485	13_32972626_A_T	2.5x10 ⁻¹¹	0
DOUBLE STRAND BREAK REPAIR	RAD51B	4,358	14_69029203_C_T	1.1x10 ⁻¹⁰	0
EPITHELIAL-MESENCHYMAL INTERACTIONS	PTHLH	1,366	12_28174817_C_T	2.3x10 ⁻³¹	49901
ESTROGEN RECEPTOR SIGNALING	ESR1	2,783	6_151985574_T_C	8.9x10 ⁻³⁹	26056
ESTROGEN RECEPTOR SIGNALING	NR2F6	187	19_17359535_C_T	9.4x10 ⁻³²	0
ESTROGEN RECEPTOR SIGNALING	CCNE1	755	19_30277729_C_T	6.8x10 ⁻⁹	25171
ESTROGEN RECEPTOR SIGNALING	NCOA1	1,426	2_24739694_C_CT	9.7x10 ⁻⁹	67651
ESTROGEN RECEPTOR SIGNALING	HNF4G	3,619	8_76360637_A_G	1.2x10 ⁻⁸	91565
ESTROGEN RECEPTOR SIGNALING	PPP1CB	575	2_28956786_G_A	1.2x10 ⁻⁸	17827
GENE SILENCING	TERT	381	5_1279790_C_T	1.9x10 ⁻⁴⁹	0
GENE SILENCING	RALB	447	2_121077184_A_G	1.2x10 ⁻¹³	24898
GENE SILENCING	TNRC6B	1,327	22_40734189_G_GA	8.3x10 ⁻¹¹	0
REGULATION OF NITRIC OXIDE METABOLISM	TERT	381	5_1279790_C_T	1.9x10 ⁻⁴⁹	0
REGULATION OF NITRIC OXIDE METABOLISM	ESR1	2,783	6_151985574_T_C	8.9x10 ⁻³⁹	26056
REPRODUCTIVE SYSTEM	INHBB	605	2_121079515_A_C	9.3x10 ⁻¹⁸	24203
RESPONSE TO CATECHOLAMINE	PDE4D	8,270	5_58429733_C_T	1.7x10 ⁻⁸	0
WNT/BETA CATENIN	TERT	381	5_1279790_C_T	1.9x10 ⁻⁴⁹	0
WNT/BETA CATENIN	TCF7L2	2,437	10_114782803_T_C	6.5x10 ⁻¹⁵	0
OTHER-NOT CLUSTERED	BABAM1	141	19_17393925_C_A	4.7x10 ⁻⁵³	0
OTHER-NOT CLUSTERED	PTHLH	1,366	12_28174817_C_T	2.3x10 ⁻³¹	49901
OTHER-NOT CLUSTERED	PLVAP	308	19_17462094_T_G	1.3x10 ⁻²⁶	0
OTHER-NOT CLUSTERED	MDM4	527	1_204518842_C_A	7.0x10 ⁻²⁶	0
OTHER-NOT CLUSTERED	PIK3C2B	533	1_204464181_C_T	1.0x10 ⁻²⁴	0
OTHER-NOT CLUSTERED	GTPBP3	118	19_17456375_TCTC_T	1.3x10 ⁻²³	0
OTHER-NOT CLUSTERED	PEX14	813	1_10566272_C_T	9.7x10 ⁻²²	0
OTHER-NOT CLUSTERED	DFFA	112	1_10537437_C_G	2.0x10 ⁻²⁰	0
OTHER-NOT CLUSTERED	INHBB	605	2_121079515_A_C	9.3x10 ⁻¹⁸	24203
OTHER-NOT CLUSTERED	CDKN2A	170	9_21963048_C_T	4.3x10 ⁻¹⁵	0
OTHER-NOT CLUSTERED	TCF7L2	2,437	10_114782803_T_C	6.5x10 ⁻¹⁵	0
OTHER-NOT CLUSTERED	RALB	447	2_121077184_A_G	1.2x10 ⁻¹³	24898

OTHER-NOT CLUSTERED	MKL1	1,176	22_40904707_CT_C	4.0×10^{-13}	0
OTHER-NOT CLUSTERED	SLC6A18	290	5_1241565_A_G	8.4×10^{-13}	0
OTHER-NOT CLUSTERED	FRY	1,573	27_CAATAAAATAAATA_C	2.0×10^{-12}	0
OTHER-NOT CLUSTERED	ATM	701	11_108098459_TAA_T	2.5×10^{-12}	0
OTHER-NOT CLUSTERED	KCNU1	3,952	8_36849946_C_G	2.8×10^{-12}	56303
OTHER-NOT CLUSTERED	ANXA13	541	8_124757661_C_T	1.7×10^{-11}	8014
OTHER-NOT CLUSTERED	KCNN4	182	19_44281824_C_CTCTT	2.7×10^{-9}	0
OTHER-NOT CLUSTERED	CFLAR	323	2_202004837_G_C	3.1×10^{-9}	0
OTHER-NOT CLUSTERED	APITD1	154	0491895_A_AGCGAGAC	4.6×10^{-9}	0
OTHER-NOT CLUSTERED	TRMT61B	217	2_29094032_C_A	8.6×10^{-9}	0
OTHER-NOT CLUSTERED	NCOA1	1,426	2_24739694_C_CT	9.7×10^{-9}	67651
OTHER-NOT CLUSTERED	ADCY3	836	2_25129473_A_G	1.3×10^{-8}	0
OTHER-NOT CLUSTERED	CDH2	5,742	18_25401204_AT_A	1.4×10^{-8}	129725

ures 14-15)

Supplementary Table 14: Pathways enri

Theme

[illegible]

ched in susceptibility to ER-negative breast cancer (enrichment score [ES]≥0.41) but

Pathway

ACTIVATION OF PROTEIN KINASE A ACTIVITY
ADENYLATE CYCLASE ACTIVATING PATHWAY
ADENYLATE CYCLASE INHIBITORY PATHWAY
CA-DEPENDENT EVENTS
CALMODULIN INDUCED EVENTS
CAM PATHWAY
CAMP BIOSYNTHETIC PROCESS
INHIBITION OF ADENYLATE CYCLASE PATHWAY
LPA4-MEDIATED SIGNALING EVENTS
PKA-MEDIATED PHOSPHORYLATION OF CREB
PKA ACTIVATION
PKA ACTIVATION IN GLUCAGON SIGNALLING
ADHERENS JUNCTION ORGANIZATION
ADHERENS JUNCTIONS INTERACTIONS
APOPTOTIC DNA FRAGMENTATION
CELL CYCLE
G2 DNA DAMAGE CHECKPOINT
MITOTIC G2/M TRANSITION CHECKPOINT
NEGATIVE REGULATION OF G2/M TRANSITION OF MITOTIC CELL CYCLE
CELLULAR RESPONSE TO GAMMA RADIATION
NONHOMOLOGOUS END-JOINING (NHEJ)
CELLULAR RESPONSE TO EXOGENOUS DSRNA
REPRESSION OF WNT TARGET GENES
ACROSOME REACTION
AMINO ACID TRANSPORT ACROSS THE PLASMA MEMBRANE
BIOCARTA_DNAFRAGMENT_PATHWAY
BIOCARTA_RARRXR_PATHWAY
BIOCARTA_SET_PATHWAY
BIOCARTA_VDR_PATHWAY
CHROMOSOME SEPARATION
INSULIN IGF PATHWAY-PROTEIN KINASE B SIGNALING CASCADE
MITOCHONDRIAL RNA PROCESSING
MYOBLAST DIFFERENTIATION
N-CADHERIN SIGNALING EVENTS
NEGATIVE REGULATION OF ESTABLISHMENT OF PROTEIN LOCALIZATION TO PLASMA
NEURONAL STEM CELL POPULATION MAINTENANCE
P38MAPK EVENTS
POSITIVE REGULATION OF GLYCOPROTEIN BIOSYNTHETIC PROCESS
POSITIVE REGULATION OF GLYCOPROTEIN METABOLIC PROCESS
PROTEIN KINASE C SIGNALING
REGULATION OF CELLULAR EXTRAVASATION
REGULATION OF HORMONE METABOLIC PROCESS
REGULATION OF MYOBLAST FUSION
TISSUE REGENERATION
TRNA THREONYLCARBAMOYLADENOSINE METABOLIC PROCESS
YAP1- AND WWTR1 (TAZ)-STIMULATED GENE EXPRESSION

Database
GOBP
REACTOME DATABASE ID RELEASE 55
REACTOME
REACTOME
REACTOME
REACTOME
GOBP
REACTOME DATABASE ID RELEASE 55
PATHWAY INTERACTION DATABASE NCI-NATURE CURATED DATA
REACTOME DATABASE ID RELEASE 55
REACTOME DATABASE ID RELEASE 55
REACTOME
GOBP
REACTOME
GOBP
PANTHER PATHWAY
GOBP
GOBP
GOBP
GOBP
REACTOME
GOBP
REACTOME DATABASE ID RELEASE 55
GOBP
REACTOME DATABASE ID RELEASE 55
MSIGDB_C2
MSIGDB_C2
MSIGDB_C2
MSIGDB_C2
GOBP
PANTHER PATHWAY
GOBP
GOBP
PATHWAY INTERACTION DATABASE NCI-NATURE CURATED DATA
GOBP
GOBP
REACTOME DATABASE ID RELEASE 55
GOBP
GOBP
GOBP
GOBP
GOBP
GOBP
GOBP
REACTOME DATABASE ID RELEASE 55

Pathway ID	Enrichment Score	Number of Genes	Genes
GO:0034199	0.52	16	ADCY3,ADCY9,F
170660	0.62	10	ADCY3,ADCY9,C
R-HSA-170670.1	0.55	14	ADCY3,ADCY9,C
R-HSA-111996.1	0.43	30	ADCY3,ADCY9,F
R-HSA-111933.1	0.42	28	ADCY3,ADCY9,F
R-HSA-111997.1	0.42	28	ADCY3,ADCY9,F
GO:0006171	0.47	16	ADCY3,ADCY9,C
997269	0.55	14	ADCY3,ADCY9,C
LPA4-MEDIATED SIGNALING EVENTS	0.55	15	ADCY3,ADCY9,C
111931	0.44	20	ADCY3,ADCY9,F
163615	0.45	19	ADCY3,ADCY9,F
R-HSA-164378.1	0.49	17	ADCY3,ADCY9,F
GO:0034332	0.44	60	CDH2,SORBS1,C
R-HSA-418990.2	0.54	29	CDH2,CDH8,CA
GO:0006309	0.45	13	DFFA,CECR2,DI
P00013	0.42	14	CCNE1,RPA3,PS
GO:0031572	0.52	29	BABAM1,ATM,I
GO:0044818	0.47	15	ATM,HUS1B,FA
GO:0010972	0.41	17	ATM,HUS1B,FA
GO:0071480	0.47	11	ATM,XRCC6,ATI
R-HSA-5693571.1	0.46	36	BABAM1,ATM,T
GO:0071360	0.46	10	RALB,COLEC12,
4641265	0.41	13	TCF7L2,AES,TLE
GO:0007340	0.47	10	ADCY3,STX2,SY
352230	0.53	30	SLC6A18,SLC6A
BIOCARTA_DNAFRAGMENT_PATHWAY	0.50	10	DFFA,CASP3,GZ
BIOCARTA_RARRXR_PATHWAY	0.48	15	NCOA1,NCOA3,
BIOCARTA_SET_PATHWAY	0.46	11	DFFA,CREBBP,A
BIOCARTA_VDR_PATHWAY	0.48	12	NCOA1,NCOA3,
GO:0051304	0.49	15	APITD1,SMARC
P00033	0.42	22	MDM4,FOXO1,I
GO:0000963	0.54	14	GTPBP3,TRMT6
GO:0045445	0.52	20	TCF7L2,MYOCD
N-CADHERIN SIGNALING EVENTS	0.41	36	CDH2,PTPN1,RH
GO:0090005	0.43	12	ANXA13,PID1,L
GO:0097150	0.57	10	CDH2,DLL1,HES
171007	0.47	12	RALB,MAPKAPK
GO:0010560	0.49	14	TCF7L2,PLCB1,F
GO:1903020	0.44	16	TCF7L2,PLCB1,F
GO:0070528	0.47	13	PLVAP,SLC26A6
GO:0002691	0.54	13	PLVAP,PLCB1,P
GO:0032350	0.42	17	TCF7L2,GATA3,
GO:1901739	0.45	10	CFLAR,CD53,M
GO:0042246	0.48	13	CFLAR,EYS,IGF1
GO:0070525	0.59	12	GTPBP3,TRMT6
2032785	0.43	29	NCOA1,HIPK1,T

PRKAR1A, PRKAR2B, ADCY1, PRKACB, ADCY2, ADCY8, PRKACA, PRKAR2A, PRKACG, PRKAR1B, ADCY5, ADCY7, ADCY4, A
3NAL, ADCY1, ADCY2, ADCY8, ADCY5, ADCY7, ADCY4, ADCY6
3NAL, ADCY1, ADCY2, GNAI3, ADCY8, GNAT3, GNAI1, GNAI2, ADCY5, ADCY7, ADCY4, ADCY6
PDE1C, PRKAR1A, PRKAR2B, ADCY1, PRKACB, PLA2G4A, CAMK4, ADCY2, ADCY8, PRKACA, PDE1A, PRKAR2A, CREB1, CA
PDE1C, PRKAR1A, PRKAR2B, ADCY1, PRKACB, CAMK4, ADCY2, ADCY8, PRKACA, PDE1A, PRKAR2A, CREB1, CALM3, PRKI
PDE1C, PRKAR1A, PRKAR2B, ADCY1, PRKACB, CAMK4, ADCY2, ADCY8, PRKACA, PDE1A, PRKAR2A, CREB1, CALM3, PRKI
CALCRL, ADCY1, ADCY2, RAMP2, ADCY10, ADM, NPR3, UCN2, GNAS, ADCY5, TAAR1, ADORA2A, ADCY4, ADCY6
3NAL, ADCY1, ADCY2, GNAI3, ADCY8, GNAT3, GNAI1, GNAI2, ADCY5, ADCY7, ADCY4, ADCY6
3NAL, ADCY1, RPS6KA5, ADCY2, ADCY8, PRKACA, PRKCE, CREB1, LPAR4, ADCY5, ADCY7, ADCY4, ADCY6
PRKAR1A, PRKAR2B, ADCY1, PRKACB, ADCY2, ADCY8, PRKACA, PRKAR2A, CREB1, CALM3, PRKACG, PRKAR1B, ADCY5, A
PRKAR1A, PRKAR2B, ADCY1, PRKACB, ADCY2, ADCY8, PRKACA, PRKAR2A, CALM3, PRKACG, PRKAR1B, ADCY5, ADCY7, C
PRKAR1A, PRKAR2B, ADCY1, PRKACB, ADCY2, ADCY8, PRKACA, PRKAR2A, PRKACG, PRKAR1B, GNAS, ADCY5, ADCY7, AI
CDH8, CADM2, ACTN2, PVR, CDH10, CDH11, CDH13, CDH4, TBCD, JUP, CTNND1, PVRL1, DLC1, CDH18, CDH12, RAMP2, C
DM2, PVR, CDH10, CDH11, CDH13, CDH4, JUP, CTNND1, PVRL1, CDH18, CDH12, CTNNA1, CDH6, CDH7, CADM1, CDH1,
CER1, KPNA1, CASP3, H1FO, DNASE1L3, HMGB2, KPNB1, HMGB1, DFFB, FOXL2, ENDOG
ME3, CCNE2, PSMD11, PSMD12, CCND2, CINP, PSMD14, PSMD7, PSMD3, PSMD13, PSMD4, CCND3
BRE, BRCA1, FANCI, FOXN3, DTL, FAM175A, PLK1, HMGA2, TAOK1, CHEK1, BRSK1, NBN, NEK6, TAOK2, MAPKAPK2, TAC
NCI, FOXN3, NAE1, HMGA2, NBN, TAOK3, CLSPN, BLM, TICRR, CDK5RAP3, CCNA2, HUS1, ZNF830
NCI, FOXN3, NAE1, HMGA2, NBN, TAOK3, FHL1, USP47, CLSPN, BLM, TICRR, CDK5RAP3, CCNA2, HUS1, ZNF830
R, XRCC5, WRN, TLK2, YAP1, TSPYL5, KDM1A, CRYAB, TMEM109
TP53BP1, XRCC6, BRE, BRCA1, FAM175A, XRCC5, SUMO1, LIG4, POLM, UBE2V2, BARD1, TDP2, RNF8, NHEJ1, HERC2, NE
IFNB1, MB21D1, TMEM173, CAV1, MAVS, MUL1, IFIT1, FLOT1
1, CTNNB1, CTBP2, HDAC1, TLE3, TLE4, LEF1, TCF7L1, TLE2, TCF7, CTBP1
T6, ZP4, ACR, ROPN1B, TNP2, PKDREJ, SPESP1, AKAP3
19, SLC38A1, SLC38A2, SLC43A1, SLC6A14, SLC3A2, SLC7A8, SLC43A2, SLC38A4, SLC7A6, SLC36A1, SLC7A9, SLC6A15, S
MB, HMGB2, TOP2A, HMGB1, DFFB, TOP2B, CASP7, ENDOG
POLR2A, NCOR2, GTF2E1, NCOA2, HDAC3, RXRA, KAT2B, GTF2F1, TBP, GTF2A1, GTF2B, RARA, ERCC3
NP32A, GZMA, GZMB, HMGB2, PRF1, DFFB, NME1, APEX1, SET
NCOA2, TSC2, RXRA, CREBBP, MED1, HDAC1, EP300, CARM1, KAT2B, NCOR1
AD1, ERCC4, M1AP, RECQL5, FANCM, TEX14, ESPL1, STRA13, NCAPD3, MEIOB, DIS3L2, TOP2A, TOP2B, NCAPD2
IGF1, IGF1R, INSRR, TSC2, IGF2, GSK3B, IRS2, TSC1, INSR, PTEN, IRS1, PIK3CA, IGF2R, FOXO3, GSK3A, INPPL1, PDPK1, MD
1B, TRNT1, PNPT1, ELAC2, KIAA0391, HSD17B10, MTO1, SUPV3L1, TRIT1, TRMU, PUS1, TRMT10C, FASTKD5
IGF1, NRG1, IFRD1, EPAS1, JAG1, GREM1, MBNL1, SDC1, RBPJ, SRF, NOTCH1, RB1, SOX15, T, REST, HINFP, MAPK12, TB
HOA, PTPN11, ROCK1, MYL2, JUP, CTNND1, GSN, AXIN1, GAP43, MAPK8, PIK3R1, FER, CTNNA1, CNR1, DCTN1, CTNNB1
RRC15, GOPC, PPP2R5A, PKDCC, RHOQ, BCL2L1, PPFA1, TMEM59, CSK, TMBIM1
5, MMP24, JAG1, HES1, PROX1, NOTCH1, SOX2, SRRT
3, KRAS, RALA, HRAS, MAPKAPK2, MAPK11, RALGDS, NRAS, MAPK14, MAPK13, MAPK12
XYLP1, IGF1, CTNNB1, RAMP1, CCR7, ARFGEF1, CCL19, CCL21, SOAT1, CHP1, SLC51B, GOLGA2
XYLP1, IGF1, RAB1A, CTNNB1, RAMP1, CCR7, ARFGEF1, CCL19, CCL21, SOAT1, CHP1, SLC51B, RAB1B, GOLGA2
i, AVP, MAS1, ZP4, PLEK, AZU1, DGKQ, ZP3, PDGFB, HTR2B, FLOT1, ADAM15
TGER4, CXCL12, OLFM4, CCL25, CCR2, RIPK3, FADD, ADAM8, CCL28, CCL21, ICAM1
BMP2, ARNT, DKK3, STC2, TRERF1, BMP6, HIF1A, BMP5, FFAR3, PAX8, WNT4, REST, STUB1, AKR1C3, HPN
YOD1, EHD1, MYF5, EHD2, MYOG, FLOT1, MYF6, MAPK14
i, LARGE, ERBB4, TEC, CPQ, TXK, NOV, APOD, KLK6, NACA, APOA5
i1B, HSD17B10, MTO1, OSGEPL1, TRIT1, TRMU, TP53RK, OSSEP, PUS1, TRMT10C, YRDC
TEAD4, TBL1XR1, CHD9, TBL1X, NCOA6, HELZ2, NCOA2, SMARCD3, RXRA, CREBBP, MED1, TEAD1, HIPK2, GATA4, RUNX

ADCY6

LM3,PRKCD,PRKCG,MAPK1,PRKCA,PRKACG,PRKAR1B,ADRBK1,ADCY5,ADCY7,CALM2,PDE1B,CALM1,ADCY4,ALCD,PRKCG,PRKCA,PRKACG,PRKAR1B,ADRBK1,ADCY5,ADCY7,CALM2,PDE1B,CALM1,ADCY4,ADCY6CD,PRKCG,PRKCA,PRKACG,PRKAR1B,ADRBK1,ADCY5,ADCY7,CALM2,PDE1B,CALM1,ADCY4,ADCY6

ADCY7,CALM2,CALM1,ADCY4,ADCY6

CALM2,CALM1,ADCY4,ADCY6

DCY4,ADCY6

CTNNA1,LAMA5,ACTN1,CDH6,CDH7,ACTB,CADM1,CDH1,RCC2,PVRL3,ZNF703,CTNNB1,PTPRK,RHOD,FERMT2,F
PVRL3,PVRL4,CDH3,CDH9,CDH17,CDH5,PVRL2,CADM3,CDH24,ANG,CDH15

JK3,FZR1,NEK11,RBBP8,PLK5,CDC14B,UIMC1,CLSPN,BLM,BRCC3,CDK5RAP3,CCNA2

3N,PIAS4,XRCC4,RIF1,WHSC1,KAT5,PAXIP1,RAD50,PRKDC,MRE11A,UIMC1,RNF168,H2AFX,DCLRE1C,UBE2N,MI

SLC16A10,SLC1A4,SLC7A11,SLC7A1,SLC38A5,SLC1A5,SLC7A3,SLC7A5,SLC7A10,SLC7A7,SLC6A20,SLC36A2,SLC3,

IM2,IRS4,INS

X2

,LRP5,CALM3,PIP5K1C,GJA1,GRIA2,CDC42,CTTN,FGFR1,PIK3CA,DAGLB,MAPRE1,CAMK2G,DAGLA,CALM2,RAC1

2,YAP1,CARM1,TBX5,WWTR1,CTGF,TGS1,KAT2B,TEAD2,NKX2-5,PPARA,TEAD3,NPPA

DCY6

RAB8B,PKP2,PVRL4,SMAD7,CDH3,PIP5K1C,CDH9,CDH17,CDH5,TAOK2,PIP5K1A,ARHGEF7,ACTG1,PVRL2,VCL,CT

DC1,BRCC3,TDP1,POLL

A1,SLC6A12,SLC6A6,SLC38A3

L,KIF5B,CALM1,PLCG1

TN,MLLT4,WHAMM,ACTN3,CADM3,TRIP6,TESK2,CDH24,ANG,CSK,CDH15,THY1

Supplementary Table 15: Enrichments* for ER- breast cancer based on summary statistics for c

Annotation [‡]	Proportion SNPs	Proportion heritability	Enrichment	P-value
SuperEnhancers, extended 500bp	0.17	0.43	2.48	2x10 ⁻⁷
SuperEnhancers	0.17	0.40	2.36	1x10 ⁻⁵
H3K4me3, extended 500 bp	0.26	0.60	2.35	5x10 ⁻⁴
H3K4me1	0.43	1.00	2.35	3x10 ⁻⁴
H3K27ac [†] extended 500 bp	0.42	0.98	2.31	1x10 ⁻¹²
H3K27ac [†]	0.39	0.81	2.07	2x10 ⁻⁷
H3K27ac [†] extended 500 bp	0.34	0.67	1.98	5x10 ⁻⁴
DGF, extended 500 bp	0.54	1.03	1.90	7x10 ⁻⁵
H3K4me1, extended 500 bp	0.61	0.91	1.49	2x10 ⁻⁴
Introns, extended 500 bp	0.40	0.57	1.43	9x10 ⁻⁴
Repressed, extended 500 bp	0.72	0.48	0.67	2x10 ⁻⁴

[‡]Of the 52 baseline genomic features described in Finucane, H.K. et al. Partitioning heritability by functions

^{*}Statistically significant after Bonferroni correction for 52 tests

[†]Hnisz, D. et al. Super-enhancers in the control of cell identity and disease. Cell 155, 934-47 (2013)

[‡]Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizc

ombined analysis of BCAC (ER-negative) and CIMBA (BRCA1 mutation carrier

al annotation using genome-wide association summary statistics. Nat Genet 47, 1228

sphrenia-associated genetic loci. *Nature* **511**, 421-7 (2014).

rs) data:

-35 (2015).

Supplementary Table 16: List of 125 SNPs associated with risk of ER-negative breast cancer

How identified	Location	SNP	MAF	OR	%FRR
Previous hit for breast cancer	1p36.22	rs616488	0.33	0.89	0.424
New hit for overall breast cancer	1p34.2	rs4233486	0.36	0.97	0.023
New hit for overall breast cancer	1p32.3	rs140850326	0.49	0.96	0.051
Previous hit for breast cancer	1p13.2	rs11552449	0.17	1.04	0.023
New hit for overall breast cancer	1p12	rs7529522	0.23	1.05	0.053
Previous hit for breast cancer	1q21.2	rs12048493	0.38	1.05	0.071
Previous hit for breast cancer	1q32.1	rs6678914	0.41	0.94	0.124
Previous hit for breast cancer	1q32.1	rs4245739	0.26	1.12	0.347
Previous hit for breast cancer	1q32.1	rs4951011	0.16	1.07	0.080
New hit for overall breast cancer	1q32.1	rs35383942	0.06	1.15	0.150
Previous hit for breast cancer	1q43	rs72755295	0.03	1.09	0.023
New hit for overall breast cancer	2p25.1	rs113577745	0.10	1.06	0.035
Previous hit for breast cancer	2p24.1	rs12710696	0.36	1.04	0.041
New hit for ER-negative breast cancer	2p23.3	rs200648189	0.19	0.94	0.072
Previous hit for breast cancer	2p23.2	rs4577244	0.23	0.93	0.125
New hit for overall breast cancer	2q13	rs71801447	0.06	1.05	0.011
Previous hit for breast cancer	2q14.1	rs4849887	0.10	0.85	0.334
Previous hit for breast cancer	2q33.1	rs1830298	0.28	1.08	0.162
Previous hit for breast cancer	2q35	rs4442975	0.50	0.94	0.129
Previous hit for breast cancer	2q35	rs16857609	0.26	1.07	0.119
Previous hit for breast cancer	3p24.1	rs4973768	0.47	1.04	0.047
Previous hit for breast cancer	3p21.31	rs6796502	0.10	0.92	0.080
Previous hit for breast cancer	3p14.1	rs1053338	0.14	1.03	0.007
New hit for overall breast cancer	3p13	rs6805189	0.48	1.00	0.008
New hit for overall breast cancer	3p12.1	rs13066793	0.09	0.96	0.010
New hit for overall breast cancer	4p14	rs6815814	0.26	1.06	0.084
New hit for overall breast cancer	4q21.23	4:84370124	0.47	1.03	0.023
New hit for overall breast cancer	4q22.1	rs10022462	0.44	1.01	0.007
New hit for overall breast cancer	4q28.1	rs77528541	0.13	0.94	0.053
Previous hit for breast cancer	5p15.33	rs10069690	0.26	1.19	0.830
Previous hit for breast cancer	5p15.33	rs3215401	0.31	0.88	0.495
New hit for overall breast cancer	5p15.33	rs116095464	0.05	1.03	0.003
Previous hit for breast cancer	5p15.1	rs13162653	0.45	0.98	0.006
Previous hit for breast cancer	5p12	rs10941679	0.25	1.03	0.016
New hit for overall breast cancer	5q11.1	rs35951924	0.32	0.96	0.042
Previous hit for breast cancer	5q11.2	rs62355902	0.16	1.06	0.057
Previous hit for breast cancer	5q11.2	rs10472076	0.38	1.03	0.020
Previous hit for breast cancer	5q11.2	rs1353747	0.09	0.98	0.005
Previous hit for breast cancer	5q14.2	rs7707921	0.25	0.97	0.016
New hit for overall breast cancer	5q22.1	rs6882649	0.34	0.98	0.002
Previous hit for breast cancer	5q33.3	rs1432679	0.43	1.08	0.200
Previous hit for breast cancer	6p25.3	rs11242675	0.37	0.99	0.005
New hit for overall breast cancer	6p22.3	rs3819405	0.33	0.97	0.022
New hit for overall breast cancer	6p22.2	rs71557345	0.07	0.91	0.069
Previous hit for breast cancer	6p22.1	rs9257408	0.41	1.03	0.020
Previous hit for breast cancer	6q14.1	rs17529111	0.22	1.06	0.075
New hit for overall breast cancer	6q14.1	rs12207986	0.47	0.96	0.051

New hit for ER-negative breast cancer	6q23.1	rs6569648	0.23	0.94	0.089
Previous hit for breast cancer	6q25	rs9397437	0.07	1.32	0.716
Previous hit for breast cancer	6q25.1	rs3757322	0.32	1.14	0.529
Previous hit for breast cancer	6q25.2	rs2747652	0.47	0.92	0.240
New hit for overall breast cancer	7p15.3	rs7971	0.35	0.96	0.046
New hit for overall breast cancer	7p15.1	rs17156577	0.11	1.05	0.025
Previous hit for breast cancer	7q21.2	rs6964587	0.39	1.02	0.003
New hit for overall breast cancer	7q22.1	rs71559437	0.12	0.95	0.029
Previous hit for breast cancer	7q32.3	rs4593472	0.35	0.97	0.019
New hit for ER-negative breast cancer	8p23.3	rs66823261	0.23	1.08	0.140
Previous hit for breast cancer	8p12	rs9693444	0.32	1.02	0.003
Previous hit for breast cancer	8p11.23	rs13365225	0.18	0.90	0.225
Previous hit for breast cancer	8q21.11	rs6472903	0.17	0.96	0.025
Previous hit for breast cancer	8q21.11	rs2943559	0.08	1.10	0.088
Previous hit for breast cancer	8q23.3	rs13267382	0.36	1.02	0.003
New hit for ER-negative breast cancer	8q24.13	rs17350191	0.34	1.07	0.139
Previous hit for breast cancer	8q24.21	rs13281615	0.41	1.07	0.150
Previous hit for breast cancer	8q24.21	rs11780156	0.17	1.05	0.039
Previous hit for breast cancer	9p21.3	rs1011970	0.16	1.05	0.037
Previous hit for breast cancer	9q31.2	rs10759243	0.29	1.02	0.003
Previous hit for breast cancer	9q31.2	rs676256	0.38	0.98	0.002
Previous hit for breast cancer	9q31.2	rs10816625	0.06	1.07	0.029
New hit for overall breast cancer	9q33.1	rs1895062	0.41	0.93	0.174
New hit for overall breast cancer	9q33.3	rs10760444	0.43	1.05	0.077
New hit for overall breast cancer	9q34.2	rs587745765	0.20	1.05	0.046
New hit for overall breast cancer	10p14	rs67958007	0.12	1.08	0.080
Previous hit for breast cancer	10p12.31	rs11814448	0.02	1.04	0.004
Previous hit for breast cancer	10q21.2	rs10995201	0.16	0.93	0.090
Previous hit for breast cancer	10q22.3	rs704010	0.38	1.06	0.108
New hit for overall breast cancer	10q23.33	rs140936696	0.18	1.04	0.022
Previous hit for breast cancer	10q25.2	rs7904519	0.46	1.08	0.202
Previous hit for breast cancer	10q26.13	rs35054928	0.40	1.06	0.108
Previous hit for breast cancer	10q26.13	rs2981578	0.47	1.04	0.045
Previous hit for breast cancer	11p15.5	rs3817198	0.32	1.02	0.003
New hit for overall breast cancer	11p15	rs6597981	0.48	0.94	0.128
Previous hit for breast cancer	11q13.1	rs3903072	0.47	0.99	0.005
New hit for ER-negative breast cancer	11q22.3	rs11374964	0.42	0.91	0.303
New hit for ER-negative breast cancer	11q22.3	rs74911261	0.02	0.82	0.102
Previous hit for breast cancer	11q24.3	rs11820646	0.40	0.94	0.123
Previous hit for breast cancer	12p13.1	rs12422552	0.26	1.04	0.035
Previous hit for breast cancer	12p11.22	rs7297051	0.24	0.87	0.499
New hit for overall breast cancer	12q21.31	12:85009437:T:C	0.34	0.93	0.162
Previous hit for breast cancer	12q22	rs17356907	0.30	0.94	0.108
New hit for overall breast cancer	12q24.31	12:120832146:C:T	0.16	1.04	0.020
Previous hit for breast cancer	13q13.1	rs11571833	0.01	1.58	0.290
Previous hit for breast cancer	13q22.1	rs6562760	0.23	0.92	0.168
Previous hit for breast cancer	14q13.3	rs2236007	0.21	0.95	0.052
Previous hit for breast cancer	14q24.1	rs999737	0.23	0.92	0.168
Previous hit for breast cancer	14q32.12	rs11627032	0.25	0.95	0.062
New hit for overall breast cancer	14q32.33	rs10623258	0.45	1.03	0.023

Previous hit for breast cancer	15q26.1	rs2290203	0.21	0.96	0.029
New hit for ER-negative breast cancer	16p13.3	rs11076805	0.25	0.92	0.178
Previous hit for breast cancer	16q12.1	rs4784227	0.24	1.14	0.441
Previous hit for breast cancer	16q12.2	rs11075995	0.24	1.07	0.111
Previous hit for breast cancer	16q12.2	rs17817449	0.41	0.93	0.174
New hit for overall breast cancer	16q12.2	rs28539243	0.49	1.05	0.075
Previous hit for breast cancer	16q23.2	rs13329835	0.23	1.06	0.077
New hit for overall breast cancer	16q24.2	rs4496150	0.25	0.96	0.036
Previous hit for breast cancer	17q11.2	chr17:29230520	0.27	0.95	0.065
New hit for overall breast cancer	17q21.31	17:44252468:G:A	0.19	0.95	0.048
Previous hit for breast cancer	17q22	rs2787486	0.30	0.96	0.040
Previous hit for breast cancer	17q25.3	rs745570	0.50	1.04	0.048
New hit for ER-negative breast cancer	18q12.1	rs36194942	0.30	0.92	0.199
New hit for overall breast cancer	18q12.1	rs117618124	0.05	0.84	0.196
New hit for overall breast cancer	19p13.13	rs78269692	0.05	1.09	0.042
Previous hit for breast cancer	19p13.11	rs67397200	0.30	1.17	0.738
Previous hit for breast cancer	19p13.11	rs4808801	0.34	0.96	0.046
New hit for overall breast cancer	19p13.11	rs2965183	0.35	1.05	0.069
New hit for ER-negative breast cancer	19p13.2	rs322144	0.47	0.95	0.085
New hit for ER-negative breast cancer	19q12	rs113701136	0.32	1.08	0.175
New hit for overall breast cancer	19q13.22	rs71338792	0.23	1.03	0.012
Previous hit for breast cancer	19q13.31	rs3760982	0.46	1.08	0.203
New hit for overall breast cancer	20p12.3	rs16991615	0.06	1.10	0.065
New hit for overall breast cancer	20q13.13	rs6122906	0.18	1.08	0.116
Previous hit for breast cancer	22q13.1	chr22:39359355	0.04	1.09	0.038
Previous hit for breast cancer	22q13.1	rs6001930	0.10	1.14	0.215
New hit for overall breast cancer	22q13.2	rs73161324	0.06	1.10	0.064
New hit for overall breast cancer	22q13.31	rs28512361	0.11	1.09	0.097

MAF, minor allele frequency; OR, odds ratio per copy of the minor allele, estimated based on OncoArray data
 %FRR, percentage explained of an assumed 2-fold increased risk of ER-negative breast cancer to the first-degree female relative of a woman with ER-negative breast cancer

Supplementary Table 17: List of 39 SNPs associated with breast cancer risk for *BRCA1* mutation ca

How identified	Location	SNP	MAF	HR
Previous hit for breast cancer	1p36.22	rs616488	0.33	0.96
New hit for overall breast cancer	1p34.2	rs4233486	0.36	0.95
Previous hit for breast cancer	1q32.1	rs4245739	0.26	1.09
New hit for overall breast cancer	1q41	rs11117758	0.21	0.94
Previous hit for breast cancer	1q43	rs72755295	0.03	1.13
New hit for ER-negative breast cancer	2p23.3	rs200648189	0.19	0.88
Previous hit for breast cancer	2p23.2	rs4577244	0.23	0.92
Previous hit for breast cancer	2q33.1	rs1830298	0.28	1.08
Previous hit for breast cancer	2q35	rs16857609	0.26	1.04
Previous hit for breast cancer	5p15.33	rs10069690	0.26	1.18
Previous hit for breast cancer	5p15.33	rs3215401	0.31	0.90
Previous hit for breast cancer	5q33.3	rs1432679	0.43	1.04
New hit for overall breast cancer	6q14.1	rs12207986	0.47	0.95
New hit for ER-negative breast cancer	6q23.1	rs6569648	0.23	0.94
Previous hit for breast cancer	6q25	rs9397437	0.07	1.20
Previous hit for breast cancer	6q25.1	rs3757322	0.32	1.14
New hit for overall breast cancer	7q34	rs11977670	0.43	1.06
Previous hit for breast cancer	8p11.23	rs13365225	0.18	0.95
Previous hit for breast cancer	8q21.11	rs2943559	0.08	1.07
New hit for ER-negative breast cancer	8q24.13	rs17350191	0.34	1.08
New hit for overall breast cancer	9q33.1	rs1895062	0.41	0.95
Previous hit for breast cancer	10q25.2	rs7904519	0.46	1.08
Previous hit for breast cancer	11p15.5	rs3817198	0.32	1.06
New hit for ER-negative breast cancer	11q22.3	rs11374964	0.42	0.91
New hit for ER-negative breast cancer	11q22.3	rs74911261	0.02	0.74
Previous hit for breast cancer	11q24.3	rs11820646	0.40	0.94
Previous hit for breast cancer	12p11.22	rs7297051	0.24	0.88
New hit for overall breast cancer	12q24.31	12:120832146:C:T	0.16	1.06
Previous hit for breast cancer	13q22.1	rs6562760	0.23	0.89
New hit for ER-negative breast cancer	16p13.3	rs11076805	0.25	0.96
Previous hit for breast cancer	16q12.1	rs4784227	0.24	1.05
Previous hit for breast cancer	16q12.2	rs17817449	0.41	0.94
Previous hit for breast cancer	16q23.2	rs13329835	0.23	1.06
New hit for ER-negative breast cancer	18q12.1	rs36194942	0.30	0.95
New hit for overall breast cancer	18q12.1	rs117618124	0.05	0.89
Previous hit for breast cancer	19p13.11	rs67397200	0.30	1.18
New hit for ER-negative breast cancer	19p13.2	rs322144	0.47	0.92
New hit for ER-negative breast cancer	19q12	rs113701136	0.32	1.05
Previous hit for breast cancer	22q13.1	rs6001930	0.10	1.06

MAF, minor allele frequency; HR, hazard ratio per copy of the minor allele, estimated based on all available CIs; %VPR, percentage explained of the variance in polygenic risk of breast cancer for *BRCA1* mutation carriers

riers

%VPR

0.06

0.09

0.23

0.09

0.07

0.35

0.18

0.19

0.05

0.86

0.34

0.06

0.10

0.10

0.38

0.59

0.13

0.06

0.05

0.21

0.10

0.22

0.11

0.32

0.20

0.14

0.42

0.07

0.34

0.05

0.07

0.14

0.09

0.08

0.09

0.93

0.26

0.08

0.05

MBA data;

